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The Canadian Medical Association Journal

Vol. 47 TORONTO, JULY, 1942 No. 1

FURTHER EXPERIENCE WITH SULFATHIAZOLE EMULSION*

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IN the March, 1942, issue of this *Journal* the authors[1] published their experience with an oil in water emulsion of sulfathiazole (M.G.H. formula). They thus introduced a new method of topical use of sulfonamides in an old and well-established "curtain drainage" medium. A wide range of application was discussed and a few illustrative cases were described. Since the first publication a large number (several hundred) of these cases have been treated and considerable experience has in consequence been gained. In a general way it may be fairly stated that this has only led to increased confidence in the principles and practice of the method. Moreover, wider fields of application have been discovered, some of these in special branches of surgery not previously explored. With additional experience has come additional knowledge of the technique, as well as information concerning the emulsion and the results of treatment. In addition, several details only tentatively referred to in our previous paper have received confirmation.

The reasons for the choice of formula have already been stated in the first report. Nevertheless, we have continued to experiment with the emulsion in its present form, as well as modifications of its base and of the sulfonamide content. Our investigations have been made both clinically and in the laboratory. Some of them have resulted from suggestions from others for which we are duly grateful. Consequently, the emulsion has undergone severe and critical scrutiny. In general, it should be stated that we have been quite satisfied to let the present formula stand unaltered as the basic sulfonamide emulsion. However, as will be demonstrated throughout this paper, certain modifications or adaptations may be advantageous or even necessary in specific cases. These exceptional instances have served rather to emphasize the usefulness and elasticity of the basic principles involved. It is a fact that our experience has only served to confirm those principles. The scope of this paper does not permit description of the details of our recent investigations, but it is desirable to summarize the results briefly.

ESTIMATION OF LOCAL TISSUE CONCENTRATIONS OF SULFATHIAZOLE

To determine the rate of delivery of sulfathiazole from an emulsion pack, and the local tissue concentration of the drug, an amount of emulsion equivalent to the maximum so far used in clinical work for curtain drainage was packed with gauze into the normal gluteal muscle of rabbits.* The wound was sutured. After 24 hours the wound was reopened, the muscle biopsied, and the specimen washed in running water and blotted. A concentration of 100 mgm. per cent was found to be present. Similarly after 48 hours the concentration was estimated and found to be 64 mgm. per cent.

In clinical cases, carbuncles and abscesses were packed with three to four ounces of the emulsion, and tissue 4 mm. in depth was removed from the wall after 24, 48 and 72 hours and analyzed. The results averaged 143, 82, and 45 mgm. per cent respectively. These analyses prove the satisfactory delivery, and high local concentration, of the sulfonamide from the emulsion for at least 72 hours. These analyses are being continued for longer periods of time. The concentrations are not strikingly high, not as high for instance as found experi-

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* Eight ounces of the emulsion containing 11.2 gm. of sulfathiazole has been the maximum for adults so far used, each ounce containing 1.4 gm.

mentally where large packs of pure crystals are used (Reed,[9] Hawkins[10]), but they are adequate, and very much greater than can be obtained by oral administration.

In contrast to the above-mentioned acute cases, similar tissue analyses from the base of old indurated granulating wounds showed the low concentrations of 1 to 1.7 mgm. per cent after 24 hours. It is not fair to assume from these very different findings that the usefulness of the sulfonamide emulsion is lost, since at least surface contamination is continually inhibited in the more chronic lesions.

Blood Concentrations from this Topical Method

Equivalent amounts of the emulsion were injected subcutaneously into 6 rats. These were then killed at hourly intervals and blood estimations done. The highest concentration occurred at the end of the first hour, being 12 mgm. per cent. At the second hour the blood showed only a trace, and thereafter was too low to be estimated.

In 4 clinical cases (2 appendix abscesses, a general peritonitis and a subdiaphragmatic abscess) where amounts of the emulsion containing 10 gm. of sulfathiazole were packed into the abdomen for curtain drainage, the blood levels were taken hourly for the first three hours and again at 12 and 24 hours. The results corresponded in general with the laboratory findings, in that the highest levels were in the first three-hour period, at the end of which they had fallen sharply, while at 12 and 24 hours not more than a trace was evident. The figures in the three-hour period averaged 3.2 mgm. per cent down to 1.3 mgm. per cent. Similar levels were carried out on two 20 per cent burn cases with the average of 3 mgm. per cent down to 2.1 mgm. per cent in 3 hours, while they were never more than 1.3 mgm. per cent after 24 hours. The explanation of the more prolonged level may be found in the larger absorbing surface. Otherwise it is not clear, as the total amount of sulfathiazole used was never as great as in the abdominal cases.

None of these clinical cases received oral or intravenous sulfonamide therapy during the test periods. It should be stated here that we have never found a blood level higher than 3.2 mgm. per cent following the topical use of an amount of emulsion containing 10 gm. of sulfathiazole.

The stability of the emulsion in extremes of climate has been tested and found to be quite satisfactory in both frigid and tropical temperatures. This is a matter of prime importance from the practical standpoint of shipment.

Sterility tests have been carried out regularly in the Montreal General Hospital, as well as at other laboratories and have been found unfailingly negative. A tendency to yellowish surface discoloration of the preparation on standing for some weeks, and even days, has been investigated, and has been found to be due to a minor degree of surface oxidation of triethanolamine from exposure to air. This does not affect the potency of the preparation. It has been observed also in saline and water suspensions to an even greater extent, without altering their effectiveness. Although harmless, we realize that is an undesirable condition and are endeavouring to prevent it.

It should be emphasized here that in the preparation of the emulsion a good colloid mill is essential. When otherwise made, as by hand, its stability is impaired.

A supply of microcrystals of sulfathiazole has been made available. A 5 per cent emulsion containing these instead of the ordinary macrocrystalline material is being tried out clinically. Our results are so far indeterminate.

Bacteriology

Before giving our own results, it is necessary to review the general bacteriological results in relation to sulfonamide therapy. Although organisms may be recovered frequently from infections under topical treatment with sulfonamides, their presence does not necessarily represent active infection. It is now recognized that this characteristic occurs even in most successful clinical cases. It may therefore be inferred that infection is controlled and the organisms although present are not active. A corollary to this, in all such local sulfonamide treatment, is that results must be judged clinically. It may be added that experience indicates the necessity for prolonging topical therapy to a point which allows a good margin of safety. When cultures are negative, generally speaking, it may at least be inferred that apart from the human error, the organisms have been rendered harmless and destroyed by phagocytosis.

Our own bacteriological results have occurred in infections caused by *B. streptococcus hæmolyticus*, pneumococcus, *B. coli* and *B. pyocyaneus*. They were poorest with the *staphylococcus pyogenes*, as is the general experience. In one debilitated burn case a hæmolytic staphylococcus

was not controlled until powdered sulfathiazole was applied daily, supplemented by the emulsion dressings for several days. Since this experience we have thought it wise to commend this technique as a routine for burned surfaces. On the other hand, this reinforcing technique has not been found essential in other clinical conditions, not even in carbuncles. It is interesting to note in this connection that impetigo yields readily to emulsion dressing.

We have had no experience so far with severe anaerobic infections, such as gas gangrene. One Meleney type of chronic leg ulcer, however, gave a highly successful result.

Saprophytic organisms are well controlled, and this is borne out by the relative freedom from odour in even long dressings up to two weeks. This corresponds with the similar results obtained when B.I.P.P. and liquid paraffin packing have been used for curtain drainage. Finally, it may be fairly stated that secondary infection has been eliminated to the extent that it may be said not to have occurred.

Observations on Curtain Drainage with the Emulsion Pack

We have been asked so frequently to explain what is meant by "curtain drainage" that we are at some pains to again comment on it and repeat references previously mentioned. The principle is an old one and was discussed thoroughly by Morrison[2] in 1918. It has been referred to frequently in the literature since then and particularly by Gurd and McKim,[3] who gave it this apt name. It is quite true that although it is an accepted and highly successful practice commonly used by surgeons, the details of how the practice operates have never been entirely explained. It has been discussed by physiologists, chemists, and physicists, as well as clinicians, and yet much remains to be understood. An interface action between the surface of the emulsion pack and the tissue surface offers material for speculation in the electrophysico-chemical field. This would be problem enough, without including the still incompletely understood specific sulfonamide effect on infections. Again there is the drainage effect of the gauze itself, and the interface drainage outwards towards the body surface. Finally to be explained is the pressure effect of the pack on the tissues, and this brings to mind the arguments about the action of pressure dressings in general and the closed plaster technique in particular.

Without presuming too much, the following explanation is suggested for sulfathiazole emulsion curtain drainage. First let us briefly review the technique. The cavity being thoroughly cleaned out with instruments and swabs, either dry or well wrung out, the depths and interstices are quite tightly packed with gauze strips of suitable width, thoroughly impregnated with the emulsion, in layer fashion, so that as the surface is approached, the packing is less tight and does not act as a cork. The whole area is then covered with a gauze dressing, either dry or emulsion impregnated as desired. The surface dressing may be changed daily or left longer, but the packing is not removed for periods varying from 3 days to 3 weeks. The ordinary redressing time of 3 to 4 days is based on the experimental observations of decreasing tissue concentration at this period, but in actual practice more prolonged periods under closed plaster technique have proved highly successful.

Now the emulsion is an oil in water one, with the sulfonamide in the water phase. It is apparent that a 5 per cent sulfathiazole emulsion which contains 24 per cent water has a much higher (25 per cent) concentration of sulfonamide in the water. Since sulfathiazole is soluble to the extent of only 0.071 per cent in water a constant saturated solution is readily maintained.* This mixes with the body fluids (serum) to become absorbed finally as sodium sulfathiazole. In the meantime the specific sulfonamide effect of combining with or neutralizing the catalytic enzymes necessary for the growth and reproduction of the bacteria goes on. The "starved" bacteria failing to multiply, may become vegetative, and are destroyed by the leucocytes and other phagocytic cells. The constant delivery of the sulfonamide from the emulsion maintains a high local tissue concentration around the packed area and makes for a continuous action. The effect of the tight packing is to keep down the local œdema and although the blood supply is maintained, lymph drainage is slowed as in any pressure dressings. The oily surface of the pack acts to shed off secretions as explained by Gurd and McKim, and this promotes drainage at the interface towards the surface. There is also some absorption of exudate by the packing gauze.

Clinical Results of Curtain Drainage with Sulfathiazole Emulsion

Many hundreds of cases have now been treated by this method in the Montreal General Hos-

* This is facilitated by the Triethanolamine.

pital. These are best discussed under general headings with a few illustrative cases.

Appendix abscesses.—Four cases, the following being typical.

M.W., a female aged 38 was operated upon on the fourth day following onset. Using a lower abdomen transverse incision, a large well walled-off abscess was found lying in the iliac fossa. The necrotic perforated appendix was in it and was removed, the stump being inverted. Considerable foul-smelling pus yielding *B. coli* was evacuated and the cavity packed with 4 inch gauze packing impregnated with the emulsion. The wound having been well wiped with the emulsion before opening the abdomen, was closed except for the lateral extremity left open for the gauze. Post-operative recovery was without incident and remarkably little discomfort. Very little discharge from the wound occurred and was odourless. On the 6th day the packing was removed without anæsthesia and the wound was clean and healthy, even the gauze tract. No suturing was done and primary healing permitted mobilization after removal of stay sutures on the 11th day. The patient left the hospital on the 16th day, the wound completely healed.

The technique employed for this and the following two abdominal cases, both as to transverse incision and as to packing of the abdomen, was that which has been described by Gurd.[4, 5]

Ruptured appendix with generalized peritonitis.—Two cases.

J.C., a male, aged 42, was admitted 36 hours after the acute onset with evident generalized peritonitis. A sub-umbilical transverse incision opened the abdomen to reveal generalized foul-smelling exudate of which a litre was suctioned off. Culture showed *B. coli.* The gangrenous, free-lying appendix was removed and the stump inverted. After abdominal toilette 3 large 4 inch packs of the emulsion impregnated gauze were placed (1) in the pelvis; (2) lateral to and below the cæcum; (3) filling the gap over the cæcum into the wound between 1 and 2. After the medial half of the wound was closed the three ends were brought out through the wound laterally, pack (3) being used to fill the unclosed gap. Post-operative recovery was uneventful, except for moderate distension relieved by the Levine tube for 3 days. The discharge from the wound was only moderate and the foul smell was missing 12 hours after operation. On the 8th day, under anæsthesia, the packs were removed and a delayed primary suture of a very clean wound was done. Primary healing occurred, though a small amount of thin serum exuded from the lateral end of the wound for 5 days. The patient was allowed up on the 16th day and discharged on the 21st day, the wound being entirely healed. The first packing contained 7 ounces of the emulsion (approximately 10 gm. of sulfathiazole).

Subdiaphragmatic abscess.—One case.

Eight days after the rupture of a duodenal ulcer, this 34-year old male was admitted to hospital, greatly distended, very dehydrated and in a serious condition. After pre-operative saline intravenous treatment and a 500 c.c. transfusion, the abdomen was opened by a transverse incision above the umbilicus. Œdematous matted adhesions prevented direct examination of the duodenum and had apparently efficiently sealed off the perforation. Exploration laterally broke into a huge subdiaphragmatic abscess, from which free gas bubbled and 2 litres of very foul-smelling thick pus and fibrin clots were removed. Culture revealed *B. hæmolytic streptococcus* and *B. coli.* Cavity was entirely lateral to and above the liver. Three large emulsion impregnated packs 4 inches in width were used and the medial half of the wound closed. Post-operative recovery was remarkably uneventful, the Levine tube caring for the distension. There was considerable discharge from the wound without appreciable odour from the first day or two. On the 6th day under general anæsthesia the packs were removed and replaced by one similar pack and the greater part of the granulating wound closed. On the 12th day this pack was removed under sedation only and an emulsion impregnated wick used to keep the shrinking cavity draining. This was removed on the 17th day and the clean granulating small residual wound in the abdominal wall sutured on the 22nd day. The patient was allowed up on the 29th day, the wound being healed. A barium drink confirmed the presence of the duodenal ulcer and the patient was discharged on the 34th day for further dietary treatment and observation.

Carbuncles.—Nine cases have been treated, all with equally satisfactory results. The following case is typical.

H.S., male, aged 54 with a large (9 cm. in diameter) 5-day old carbuncle on the neck was admitted to hospital with a fever of 102° in a very toxic state. The urine contained no sugar but the blood sugar was 0.135 mgm. per cent. Under cyclopropane anæsthesia the carbuncle was incised crucially and the flaps undercut to the edges. Culture showed *Staph. pyogenes aureus.* It was packed with 2 inch sulfathiazole emulsion gauze and dressed. The patient refused all sedatives during the post-operative period, stating that he had no pain. The outer dressings, which are so often soggy with hæmorrhagic discharge in the first 24 hours, needed no reinforcement or change and were left for 48 hours, before the first dressing. On the 4th day the pack was removed and replaced without discomfort. The old pack was soft and moist, and the necrotic material commonly found was almost completely liquefied and came away with it. The base of the carbuncle was clean granulating tissue and did not bleed. The flaps had no œdema, were quite soft and there was no persistent surrounding induration. Culture was feebly positive. The mobility of the neck was noteworthy at this stage. The second pack was removed on the 8th day when healing was so advanced that only a surface dressing with the emulsion was necessary. The patient was discharged the same day. By the 16th day a small dry dressing was sufficient and this was removed entirely on the 20th day, the wound being entirely healed. Oral sulfonamide was not used at any time, nor was insulin given.

Acute and chronic osteomyelitis.—Four cases, one acute and three chronic.

These cases were all treated by excision of necrotic bone, guttering and packing with tightly placed emulsion gauze and closed unpadded plaster technique (Gurd,[6] Trueta[7]). The post-operative course was uneventful in each case and the absence of pain fever and reaction noteworthy. Redressings have varied from 2 to 3 weeks, during which time the absence of odour has been most welcome to all concerned. Healing in all four cases has been rapid and the only noteworthy incident was the development of a hypersensitive drug rash in one case in the 9th week. This was overcome and the treatment continued by using a 5 per cent sulfadiazine emulsion. It is felt that the use of a sulfonamide emulsion forms a useful contribution to the closed plaster treatment.

Hand infections including thenar and palmar abscesses.—A large number of hand abscesses have been treated by this method with success equal to the case described in our first paper. It is felt that in this field of surgery the method has been most successful, in elimination of infections, lack of pain, and rapid healing with minimum disability.

Compound fracture with much tissue destruction.—Only one case of a long bone, a tibia, has been so treated as above-mentioned, using the closed plaster technique (Gurd[7]). Infection did not occur and the wound healed by granulation. The patient is still under treatment and bone healing is progressing at a normal satisfactory rate. Several compound fractures of the hand, etc. have shown very good results.

Open amputations.—The method has been remarkably successful in many small bone and two traumatic lower leg amputations at the site of election. In the two latter cases the closed plaster fixation was used and felt to be most advantageous. Both men had prostheses at two months. The men were at work during the 3rd month.

Ulcer cruris (Meleney type).

M.C., a stout female, aged 55, had suffered from recurring ulcers around both ankles for 15 years. The left had been healed for several years. On the right ulceration had persisted for the past five years with marked œdema and brawny induration extending halfway up the leg. The ulcer was the size of a 50-cent piece with cartilaginous edges and a dirty necrotic base. There had never been any varicose veins. Culture yielded a micro-aerophilic hæmolytic streptococcus. The Wassermann was negative and the blood sugar normal. Under bed rest and emulsion dressings healing was so rapid that the patient was mobilized and allowed to leave the hospital with an emulsion dressing under elastoplast on the 9th day. At this time the ulcer was the size of a small one-cent piece with little marginal induration, and a clean base. Dressings were changed weekly thereafter, the ulcer was completely healed on the 41st day.

Skin grafting of all kinds.—Referred to in section on burns.

Large and small infected wounds.—Both traumatic and operative. These included one large thoracic wound following a cautery lobectomy.

Minor surgery.—A large number of furuncles, abscesses, large and small, other minor surgery in general in our Out-Patient Department.

The results of treatment in 87 operative gynæcological cases were reported in some detail by one of us (Wilson[1]) in our first report. A very large number of additional cases have since been added to the series with equally satisfactory results.

Emulsion packing has been used in the otolaryngological department in a number of operations including radical mastoidectomy, and sinus operations. The results briefly stated have shown particularly rapid healing without exception and have been excellent.

The Ophthalmological Department has also had considerable experience with the emulsion and is enthusiastic in its use as a packing following ablation of the eye. It is also a useful substitute in blepharitis, in burns and otherwise (see Burns section).

BURNS

Local treatment of critical areas and infections.—About 100 major and minor burns of second and third degree have been treated in the hospital wards and outdoor department without any evidence of general infection or sepsis. Moreover, in only one case did local infection (hæmolytic staphylococcus) impede healing. As a result of the absence of infection the average healing time has been hastened. For instance, the second degree burns were discharged completely healed in from 12 to 14 days on the average. In third degree burns the absence of infection promoted healthy granulation and early healing with or without skin grafting.

Included in this series were nine cases in which infection had already occurred from neglect or delay. These were treated exactly as the others and on the fourth day showed clean areas which healed quite as rapidly as the average. The treatment is recommended for all burns on critical areas.

Emulsion technique for burned surfaces.

1. Clean the burned area mechanically (preferably without anæsthesia, using morphine sedation).
2. Lavage gently with sterile saline.
3. Spray on powder* until a good "frosting" is present.
4. Apply single layers of emulsion impregnated strips of finely meshed, sterile gauze of 1 to 2 mm. curtain mesh (sulfa-mesh). These strips may be cut to size and impregnated at the time of dressing or they may be previously sterilized and prepared in containers of various sizes.
5. Over the strips apply ordinary gauze dressings (not too thick) thoroughly impregnated with the emulsion.
6. In early stages particularly, reinforce with dry absorbent material (cotton, cellu-cotton, ordinary cotton waste, etc.) with or without pressure bandage.
7. Bandage, or use porous mitten mask or towel.

Adequate splinting with moulded plaster strips or other padded material for the extremities.

It is important to recall here that it has been shown clinically that this type of dressing with or without pressure bandage and splint provides for only minimal decrease in serum loss.

* Although not essential for first dressing, or even later, it has been found useful in redressing some cases, to spray on sterile sulfathiazole powder from a nebulizer or shaker before applying "sulfa-mesh". The sulfonamide powder may be varied according to the presence of any persisting organisms on surface, *i.e.*, sulfapyridine for bacillus proteus. (This may also be used in other types of cases with equal advantage).

The time of the first redressing is decided by the condition of the dressing, *i.e.*, whether there is much serum loss or whether further cleaning is desirable. It may therefore vary from one to seven days, generally more frequently in the first week. From laboratory and clinical experiences in local tissue concentration, and because the staphylococcus is so frequently involved, it is considered advisable to make five days the time limit for changing burn dressings in deep second and third degree burns.

The dressing has an immediate and continued local anæsthetic effect. This decreases shock and minimizes the necessity for sedatives. The explanation is not known, but the effect has been noted by many other observers with sulfonamides. It has been suggested that it is due to the molecular similarity of sulfonamides to benzocaine.

The dressings are comfortable, soft and pliable and do not themselves appreciably restrict joint movement. This makes the treatment satisfactory across joint flexures and around body orifices (all critical areas). It should also be noted that the emulsion is innocuous to the conjunctiva, an advantage in face dressings. It may be noted that on change of dressing there is no crusting and the débris largely comes away with the dressing leaving a relatively clean surface without discoloration. This permits inspection and adequate estimation of the condition of the area. Serum loss with this method though not decreased is not excessive.

Because healing is hastened early skin grafting is encouraged. To quote Dr. John Gerrie, plastic surgeon on our staff recently returned from two years' experience in Britain:

"We look for a suitable burn dressing usable from the start, especially on the face, around orifices, on extremities and across flexures. Such a dressing should be comfortable, control infection, be easily applied and removed and promote a suitable site for skin grafting. The M.G.H. emulsion has the desirable features for such a dressing. It is anæsthetic to a degree and controls infection. It is easily applied, comfortable and easily removed and promotes a beautiful, clean granulating surface for skin grafting."

The emulsion dressing has been applied directly over both Riverdin and Thiersch grafts, all of which have thrived. There has been little exudate, no infection and no odour. This offers convincing evidence against any local tissue toxicity from sulfathiazole. On the contrary, the reverse appear to be true, since the grafts do remarkably well. This may be accounted for by the absence of infection. It has also been used on donor areas with equally satisfactory results. It is perhaps of some interest to state that the method has been used in three frost-bite cases with vesication. The results were entirely satisfactory and the anæsthetic effect was welcomed by the patient.

It should be pointed out that the use of the emulsion as a burn dressing is not intended to replace tannic acid or other eschar protective coverings necessary to prevent serum loss in large surface burns on the torso. On critical areas, however, where the problem of the prevention of contractures and disability precludes the use of the eschar method, these dressings are indicated, as they do not inhibit movement, are relatively painless and may be changed readily with minimal bleeding.

Certain practical points over and above the bacteriostatic effect deserve emphasis. These dressings provide an efficient continuous treatment throughout from the emergency dressing to the completion of healing with or without skin grafting. Moreover, the simplicity of the method makes it unnecessary to have special equipment or expert attendants, while there is an economy of nursing, dressings, clothing, linen and medical care. The lack of odour and cleanliness of the dressing is a great advantage to patient, nurse, doctor and hospital. The cost of the preparation is relatively small and the materials are available even under present restrictions. Should triethanolamine become impossible to obtain equally useful substitutes are available. The dressings are comfortable, being anæsthetic to a considerable extent, are soft and do not splint joints. To sum up finally, the healing of burns is hastened by bacteriostasis, separation of the necrotic surface is accelerated by the softening effect, granulation tissue is stimulated and thus the recovery period is shortened, whether grafting be necessary or not.

N.B.—Recent experience with the emulsion dressings for burned "critical areas" has shown that the technique described herein may be satisfactorily used with pressure dressings.

The authors wish to express their thanks to Drs. Gurd, Campbell, Hodge, Ramsey and Fowler for their helpful co-operation, and to Mr. Frank Zahalan for his continued valuable assistance. Thanks are also due to Charles E. Frosst & Co., in particular, Dr. E. Lozinsky, to the Ciba Co. and Smith, Kline & French Laboratories, Philadelphia, for material and other most useful help.

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THE USE OF SULFATHIAZOLE WITH PRIMARY MASTOID WOUND CLOSURE*

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AFTER the usual so-called "simple" mastoidectomy with partial closure and healing by granulation begins a long, trying convalescence. The words of Jones,[1] "From the patient's viewpoint, the convalescent period overshadows the oblivion of the actual operation", are not exaggerated. Considerable local pain and headache is usually present, while, for four or five days, the patient experiences great difficulty in moving the head. The first dressings with repacking are quite painful and often necessitate an anæsthetic. The granulating mastoid wound frequently discharges for three to six weeks. In a series of 50 cases reported by Kreutz and Witter[2] the post-auricular wound averaged 28.5 days of dressings. Debilitated infants and children often require several months to heal. One may add to this the poor cosmetic results in some cases with a deeply depressed scar and the occasional permanent fistula. In some instances the middle ear never entirely ceases discharging. There is no doubt that new infection is often introduced into the mastoid cavity with these dressings, tending to prolong the process of healing.

In the past many different kinds of antiseptics and methods of dressing have been tried to hasten mastoid closure, with indifferent results. In 1906 Blake[3] introduced the "blood clot" operation in which the mastoid cavity, after having been allowed to fill up with blood, was completely closed without drainage. He and other otologists claimed a high percentage of primary union. However, this procedure has been abandoned, since most mastoid wounds treated in this manner subsequently break down.

Since the introduction of the sulfonamides into medicine, many articles have appeared in the literature testifying to the excellent results obtained by their local use both in clean and infected wounds. Diveley and Harrington[4] used sulfathiazole crystals in both acute and chronic osteomyelitis with good results. In mastoid wounds the local use of sulfathiazole was first suggested by Osgood.[5] Using sulfathiazole impregnated gauze packing, Guerry and Putney[6] averaged 14.9 days necessary for mastoid healing in 20 cases, as compared with 31.6 days in 20 controls dressed in the usual manner. DeWeese (quoted by Maxwell[7]) performed 10 mastoidectomies, filling each wound with sulfathiazole powder and inserting a gauze drain. Cultures from these wounds remained negative for streptococci until after the first dressing was done on the fourth or fifth day. Then streptococci and staphylococci began to appear in all the wounds. It may be noted that all such redressings were done without the reinsertion of sulfathiazole. Maxwell has suggested that the wounds were re-infected in dressing in spite of the aseptic technique used.

Livingston[8] was the first to introduce local sulfonamide implantation in mastoid wounds with complete closure. Sulfanilamide or sulfathiazole powder was used, followed by the use of the drug orally in some cases. His results were excellent. Of 13 cases, 11 healed by primary intention, one had some further serous discharge after primary union had taken place, while only in one case did breaking down of the wound occur with a moderate amount of purulent discharge. A dry middle ear resulted in every case. In commenting upon these cases, Maxwell[7] expressed the opinion that primary suture of the complete mastoid wound is not an entirely safe procedure since small infected cells may remain after any well-done mastoidectomy.

In this report a series of 16 simple mastoidectomies is presented, in which sulfathiazole crystals were implanted in the mastoid cavity

* From the Oto-Laryngology Services of the Montreal General Hospital and the Montreal Children's Hospital.

followed by complete wound closure. These cases represent all the mastoid operations done by this method at the Montreal General Hospital and the Montreal Children's Hospital in the first four months of this year.

PROCEDURE

In each case the mastoidectomy was done in the usual manner. After all débris had been removed from the wound, sterile sulfathiazole crystals were placed in all parts of the cavity and the wound edges were completely sutured together. Care was taken to disperse the powder evenly throughout the wound, to obviate clumping. The amounts used varied from one gram in infants to 8 grams in adults. In most cases after operation sulfathiazole was given by mouth in moderate doses. However, in view of the high concentration of the drug developed in the immediate vicinity of the wound, this latter procedure would appear to be unnecessary. In those cases in which it was not used little difference in the post-operative course was observed. Sutures were left in until about the ninth day, since premature removal in several cases had resulted in slight separation of the skin edges. In 3 cases which had chronic suppurative otitis media sulfathiazole powder was insufflated into the middle ear cavities every two or three days post-operatively.

CLINICAL ANALYSIS

In all 16 mastoidectomies were performed in 14 cases, and of these 2 were in adults and 12 were children. Bilateral involvement was present in 2 of the children. The children ranged in age from 5 months to 14 years. Eight of the 10 acute cases had a sub-periosteal abscess. Three others bordered on chronicity, having had aural discharge for about 3 months. The remaining 3 had chronic ears of 5 to 10 years' duration, one with an acute exacerbation. These ears showed total drum destruction with little middle-ear involvement, and were thought suitable for simple mastoidectomy. In 6 instances the dura was exposed either by necrosis or by surgical removal of softened bone.

Complete culture findings are shown in the accompanying table. It may be seen that, of the 8 acute cases with positive results, the offending organism was B. hæmolytic streptococcus in 6 instances and pneumococcus type I

TABLE I.

Case	*Name*	*Age*	*Duration of symptoms*	*Diagnosis and associated conditions*	*Culture*	*Wound healing*	*Post-operative aural discharge*
1.	R.W.	7 years	4 weeks	Acute mastoiditis; sub-periosteal abscess.	B—Hæmolytic streptococcus.	Primary.	Slight, 7-8 days.
2.	D.W.	2 years	6 weeks	Acute mastoiditis; sub-periosteal abscess.	Lost.	Slight separation, healed on 13th day.	Slight, 7 days.
3.	C.B.	2 years	3 months	Subacute mastoiditis.	*Staph. pyogenes; H. influenzæ.*	Suture pulled out. Healed on 21st day.	Slight, 8 days.
4.	Mrs. L.	42 years	5 weeks	Acute mastoiditis.	Pneumococcus III.	Primary.	Very little, 3 days.
5.	M.S. (right)	1 year	3 months	Subacute mastoiditis; pneumonia.	*Staph. pyogenes; H. influenzæ.*	Slight separation, healed on 13th day.	Moderate, 21 days.
	M.S. (left)		3 months	Subacute mastoiditis.	*Staph. pyogenes;* diphtheroids.	Primary.	Slight, 8 days.
6.	J.G.	10 years	2 weeks	Acute mastoiditis.	B—hæm. strep.	Primary.	Slight, 7-8 days.
7.	Y.M.	9 months	10 days	Acute mastoiditis; sub-periosteal abscess.	B—hæm. strep.	Primary.	Slight, 7-8 days.
8.	L.P.	18 months	2 days	Acute mastoiditis; sub-periosteal abscess.	B—hæm. strep.	Slight separation, healed on 16th day.	None.
9.	H.C.	28 months	3 weeks	Acute mastoiditis; sub-periosteal abscess.	No growth.	Primary.	Slight, 5-6 days.
10.	Mrs. Z.	36 years	6-7 weeks	Acute mastoiditis.	B—hæm. strep.	Primary.	Slight, 3 days.
11.	M.M.	9 months	6 weeks	Acute mastoiditis; pneumonia; sub-periosteal abscess.	B—hæm. strep.	Slight separation, healed on 14th day.	Moderate, 15 days.
12.	R.D.	5 months	6 weeks	Acute mastoiditis; sub-periosteal abscess.	Pneumococcus I.	Primary.	Slight, 7 days.
13.	J.A.	12 years	5 years	Chronic suppurative otitis media with acute exacerbation.	No growth (dried swab).	Slight separation, healed on 8th day.	Slight, 9-10 days.
14.	W.D. (right)	14 years	10 years	Chronic suppurative otitis media.	*B. Proteus.*	Primary.	Still slight at end of 3 weeks.
14.	W.D. (left)		10 years	Chronic suppurative otitis media.	*B. Proteus. B. Pyocyaneus.*	Primary.	

and III respectively in the other 2 cases. The subacute and chronic cases showed a variety of organisms.

It is interesting to note that of the 13 ears showing acute or subacute involvement none had oral sulfonamide therapy early in the course of the otitis media. Two of these cases had late treatment. A woman (Case 10) 4½ months pregnant, after having had aural discharge for almost 6 weeks was given 300 grains of sulfadiazine during the 5 days before operation without result. In a 12 months' old baby (Case 5) with pneumonia and bilateral otitis media of 2 months' duration, sulfathiazole cleared up the pneumonia, but exerted little influence upon the ear condition and bilateral mastoidectomy became necessary.

In the appended table are listed the salient features of each case.

RESULTS

Post-operative pain and discomfort were surprisingly slight in every case. This was especially noticeable in the older patients, particularly the lack of the usual difficulty in moving the head. These older patients were able to sit up in bed after 24 hours without assistance and were allowed up by the third or fourth day. It is a notable fact that after the first night sedatives were rarely needed. With the exception of one infant with a pre-existing pneumonia, temperatures were normal or only slightly raised after 48 hours.

Wounds.—The simple dry surface dressings gave little trouble on changing, and as a rule few re-dressings were necessary before healing was completed. After the first few cases sutures were left in until about the ninth day. In no instance did breaking down of the wound occur. Of the 16 mastoids primary union took place in 10, while slight separation of the skin edges with no communication with the mastoid cavity occurred 5 times. This did not unduly prolong healing, which took place from the eighth to the sixteenth day. One child which succeeded in pulling off its dressing, tore out two sutures. This caused considerable gaping of the lower angle of the wound, but healing was complete at the end of 21 days. The final cosmetic result was good in every instance. In one case (4) a bleb appeared in the scar line three weeks after operation. About one c.c. of turbid serosanguinous fluid was aspirated and found to be sterile.

Aural discharge. — Aural discharge in the acute cases was usually slight and a dry ear resulted in from 3 to 10 days. Of the 3 subacute cases, 2 dried up rapidly, while in the third, slight discharge persisted for 3 weeks. One of the chronic ears (Case 13) was totally dry by the twelfth day and has remained so 10 weeks after operation. Case 14, with bilateral chronic otitis media, still has slight aural discharge at the present time, three weeks postoperatively.

ILLUSTRATIVE CASE

CASE 4

Mrs. L., aged 42. Five weeks before admission she had discharge from the right ear following a cold. This continued in moderate amounts without pain for 3 weeks and then stopped. Pain behind the ear then came on gradually. Swelling also occurred and slowly extended down into the neck. Deafness was marked. Admitted March 21, 1942. Temperature 99°; pulse 88; white blood cells 10,700. The external canal was obstructed by a furuncle and the drum could not be seen. No pus was present in the canal. A considerable amount of swelling and œdema was present over the mastoid area extending down into the neck muscles. Tenderness was marked. X-ray showed complete obliteration of cellular details and extensive breaking down of the tip cells. Operation on March 24th. Very extensive pneumatization. Marked zygomatic, retrofacial, post-sinus and tip cellular development. Necrosis of the tip had exposed the sternomastoid and digastric muscles which were somewhat gangrenous. Complete cellular breaking down was found. Granulations were extensive, pale and dirty. Little pus was present. Cells extended far forward about the jugular bulb. Bony necrosis had exposed several areas of the middle fossa dura as well as small portions of the lateral sinus and jugular bulb. After complete cellular exenteration the cavity was filled with 8 grams of sulfathiazole powder and the wound edges were sutured together completely. The organism recovered on culture was pneumococcus, type III. The patient sat up in bed the next morning, having no difficulty in moving the head. No pain was present and she said that her head was only a little sore. She was out of bed on the fifth day. The highest post-operative temperature was 99°. The wound edges healed by primary intention and slight serous aural discharge lasted only 3 to 4 days. A total of 330 grains of sulfathiazole was given by mouth over 7 days. Three weeks after operation a small bleb appeared in the scar line. About 1 c.c. of turbid serous fluid was aspirated and was found to be sterile. At the present time, two months after operation, the cosmetic result is excellent and the drum is normal.

COMMENT

In any large reported series of cultures taken from mastoid wounds well over 90 per cent of the organisms recovered belong to the hæmolytic streptococcus, staphylococcus pyogenes, or pneumococcus groups. With this in mind, sulfathiazole was chosen, since accumulated evidence shows that, with the possible exception of sulfadiazine it has the most universal bacteriostatic action of any of the sulfonamides. Osgood[5] makes this statement,

"Sulfathiazole is equal or superior to sulfanilamide against the beta-hæmolytic streptococcus and equal or somewhat superior to sulfapyridine against the pneumococcus. Sulfathiazole is far superior to either sulfanilamide or sulfapyridine in staphylococcic infections, is much superior to sulfanilamide against the alpha hæmolytic streptococcus (streptococcus viridans) and is effective against many organisms, including among others, the typhoid bacillus, the paratyphoid bacillus, the colon bacillus, staphylococcus aureus and staphylococcus albus, against which neither sulfanilamide nor sulfapyridine is very effective."

The increased effectiveness of sulfathiazole locally is due to the very high concentration developed in the immediate tissue around the wound. Moreover, the relatively slow absorption of sulfathiazole allows a high concentration to remain locally for several days. Reed and Orr,[9] in experiments on guinea pigs, implanted small amounts (0.15 gm.) of sulfathiazole in muscle tissue. He found average concentrations of over 700 mgm. per cent in the tissue immediately surrounding the wound. By the end of 24 hours this had only decreased to a level of 300 mgm. per cent. This high concentration in the wound vicinity therefore nearly approaches saturation and its diffusion from these tissues into the blood is fairly slow. Also since concentrations in the general body tissues approximate that of the blood stream, it follows that the highest tissue levels (12 to 15 mgm. per cent) which can be produced with safety by mouth are only a small fraction of that possible by the local use of the drug. In addition the blood concentration occurring after absorption from local implantation is negligible. In the cases of Hawking and Piercy[10] blood levels ranged from a trace to only 2 mgm. per cent, which is an extremely safe level and probably generally nontoxic to the patient. Key[11] has stated that the local use of sulfathiazole causes no appreciable interference with wound-healing unless too much of the drug is used. Reed and Orr[9] do not believe that the natural immunizing processes are inhibited by its action. Some six of our cases, five of whom were infants, showed a tendency to separation of the skin edges in the early stage of healing. With this exception no difficulty in wound healing was encountered. Possibly some significance may be attached to this tendency to delayed union in infants.

When compared with previous methods with open drainage, the results are strikingly satisfactory. The same end-results are accomplished in a shorter period of time, with only slight discomfort to the patient. Dressings are few and almost painless, while hospitalization and convalescence are shortened. This has considerable economic importance. The almost total absence of pain after the operation is most outstanding. This is probably due to the fact that lack of packing greatly lessens tissue reaction and wound tension. In addition the analgesic action of sulfathiazole is gradually being appreciated. This action is stressed by Ackman and Wilson[12] in using an emulsion of sulfathiazole for curtain drainage and the treatment of burns.

Objections will naturally be raised to the closing of mastoid cavities in the presence of infection. While this type of procedure has been safely carried out in almost all other parts of the human body, the close proximity of the cranial cavity and the meninges to the mastoid air cells complicates the problem. The following questions must be considered: (1) dural exposure; (2) pneumococcus Type III infection; (3) the presence of infected cells, which cannot possibly be exenterated in the course of the ordinary mastoid operation.

Dural exposure.—In the course of mastoid surgery the dura is found exposed by bony erosion or is uncovered surgically in a fairly large percentage of cases. Being very resistant, complications seldom occur in spite of infection which remains in the wound for some time. In the presence of a high local concentration of sulfathiazole any exposed dura is probably now much safer than under drainage alone, while complete closure of the wound protects it from new infection. In Livingston's series 5 cases had dural exposure while 6 exposures in this series occurred without subsequent trouble.

Pneumococcus Type III infection.—Intracranial complications occur in pneumococcus Type III invasion of the mastoid relatively much more frequently than in any other infection. Because of its extreme insidiousness mastoid infection is often unrecognized until a fatal meningitis has developed. However, if the mastoiditis is recognized early, surgical intervention is usually followed by uneventful recovery (Persky[13]). No reason for apprehension in closing this type of case can be seen, providing that care has been taken in removing all infected cells possible. This care must be exercised fully, since this organism has a predilection for extensively pneumatized mastoids. However, Persky warns that all cases with this infection should be observed for three to six months after operation since late intracranial

complications can occur. Our single case of this type of infection had a rapid convalescence.

Unopened cells.—In all temporal bones there are many groups of cells having no direct communication with the mastoid cells, or which are so placed in the petrous portion as to be difficult of direct access during mastoidectomy. The fate of these cells if infected is important. Many of them, especially those situated anteriorly in the petrous apex, or about the carotid artery and the Eustachian tube, as well as some of the perilabyrinthine cells, drain directly into the middle ear (Lindsay[14]). Others of the various perilabyrinthine cell-groups may communicate with the mastoid cavity by way of the periantral cells. These periantral cells, if infected, are usually reached directly from the mastoid cavity. Undoubtedly many of the infected cells of the other groups heal spontaneously after the bulk of the mastoid cells has been exenterated. Some of them, however, may become walled off from the mastoid or middle ear producing petrous suppuration and may require special surgical procedures to drain them. Often petrositis comes to light only after the original mastoidectomy wound has healed. In the great majority of Lindsay's[15] cases of petrositis a fistula could not be traced from the mastoid cavity to the infected cells in the petrous area, either grossly at operation, or, microscopically, after post mortem. Primary closure of the mastoid cavity under such conditions would probably not affect the course of an unsuspected or latent petrositis. Small unopened cells in the immediate vicinity of the wound cavity might even be more beneficially influenced by the presence of a high concentration of sulfathiazole which could diffuse into them, than by any possible remote drainage. However, it is probable that these controversial questions will be more satisfactorily answered as more cases are reported.

SUMMARY

Complete primary closure, using implanted sulfathiazole crystals was carried out in 16 mastoidectomies.

Primary healing of the wound took place in 10 cases. In 5 cases with slight separation of the skin edges primary healing was delayed until the 8th day to the 16th day without infection. Moderate gaping of the lower angle of the wound prolonged healing until the 21st day in one case.

The duration of aural discharge in the acute cases was comparatively lessened.

Marked improvement in post-operative comfort and greatly shortened convalescence resulted.

I wish to thank Dr. G. E. Hodge for his permission to carry out this work at the Montreal General Hospital. I also wish to thank Drs. Gavin Chisholm, A. O. Freedman, V. Heney and G. E. Hilton for their permission to report the eight operations of this series which were performed by them.

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Following a lengthy discussion in *The Times* and other papers of the problem of the birth rate, Lord Horder, President of the Eugenics Society, and Mr. R. H. Titmuss, Acting Editor, *Eugenics Review*, have pointed out two popular misbeliefs: (1) that the German birth rate is increasing and that Nazis have succeeded in raising fertility to an adequate level, and (2) that family allowances and other economic measures would result in a rise in the birth rate, a belief which finds no support in evidence from countries which have instituted such schemes. Lord Horder and Mr. Titmuss point out that the German birth rate has fallen to such an extent that 150,000 fewer children were born in 1940 than in 1939. In Italy, despite a campaign dating back to 1927, the birth rate continues to decline. They believe that what is needed to bring about an increase in the birth rate is to create an environment in which people will desire children and in which this desire will not be frustrated and beset by other less attractive motives. They refer to the views of the Population Investigation Committee, 1939, that a survey of the picture of social life in England today impresses the observer with the number and excellence of the reasons why married couples should have few children and that the birth rate may well prove to be incapable of effective resuscitation until drastic changes for the better have been introduced into our social and international life.—*J. Roy. Inst. of Pub. Health & Hyg.*, 1942, **5**: 92.

SEX HORMONES IN OBSTETRICS AND GYNÆCOLOGY*

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THE purpose of this paper is to present an exposition of the functions of sex hormones, to compare their activities where these are known, and to illustrate what has been our experience with them in specific disorders.

A clear understanding of the sex cycle is an essential antecedent for the rational therapy with the newer synthetic sex hormones. It is now well established that at puberty certain hormones secreted by the pituitary gland (gonadotropins) stimulate the gonads, initiating and controlling Graafian follicle maturation, ovulation, and corpus luteum formation. As a consequence, the ovary elaborates œstrogens from the follicles and progestogens from the corpus luteum. In the male the interstitial tissue is stimulated to produce androgens. This phenomenon occurs cyclically during the period of sexual maturity in the female, and the structural and secretory changes in the ovaries are reflected in periodic alterations in the endometrium and myometrium, in the vaginal mucosa and in the mammary glands.

The œstrogenic hormone initiates and controls the functional activity of the female organism. Secreted in sufficient amount, it produces the so-called proliferative phase of endometrial development, increases the secretory activity of the uterine serous glands, enhances the contractility of the myometrium, and causes proliferation of the mammary duct system. When ovulation occurs at about the mid-interval of the cycle, the follicle ruptures and is converted into a corpus luteum. As this develops it secretes a progestogen. The period of activity of the corpus luteum is about fifteen days, and the progestogen secreted during this time converts the vascular proliferated endometrium into a functional secretory type. This prepares the endometrium for nidation of the ovum which is travelling down the Fallopian tube toward the uterus. The progestogen nullifies any further action of œstrogen, thus producing relaxation of the myometrium. It also stimulates acinar development in the mammary gland. Changes paralleling these in the endometrium take place in the vaginal mucosa and offer a basis for some diagnostic procedures in evaluating ovarian hormone function.

If ovulation is followed by fertilization, the duration of corpus luteum activity is prolonged and a decidua is formed. If fertilization does not occur the corpus luteum degenerates, and as a direct consequence degenerative changes take place in the highly specialized endometrium, resulting in its shedding or menstruation. This is associated with involutional changes in the mammary gland. The cycle is then repeated. If fertilization occurs and pregnancy follows a placenta is formed. At the end of the third lunar month the placenta takes on the function of an endocrine gland and secretes large amounts of progestogen. This tends to stabilize pregnancy.

Classification, nomenclature and physiological action.—Table I summarizes some of the known data. Pituitary gonadotropins stimulate ovarian and testicular activity in hypophysectomized animals. There is no evidence of their value in pituitary-ovarian deficiency in human beings. Whether this is due to impurities or to ineffective dosage is difficult to say. At the present time they are clinically impracticable.

Gonadotropins obtained from pregnant mare serum contain for the most part the follicle stimulating factor (FSH) and have been used extensively as substitutes for anterior pituitary preparations. These stimulate ovulation in human beings, but since they are impure and of equine origin, the possibility of an anaphylactic reaction needs to be kept in mind. Clinical usefulness of these has still to be proved.

Gonadotropins from pregnancy urine are products of the chorionic cells. Large amounts are excreted in pregnancy, ectopic gestation, hydatid mole, chorionepithelioma and carcinoma testis. The extracts contain more of the luteinizing factor (LH) than they do of FSH and

* Abridgement of a paper read at the Annual Meeting of the Canadian Medical Association, Alberta Division, Edmonton, September 11, 1941.

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consequently tend to suppress menstruation. In sufficient dosage they are of some value in functional uterine bleeding. Unfortunately, the amount which can be administered often falls short of the physiologically effective dose, limiting the clinical value. The same is true of the gonadotropins from menopausal urine which are composed principally of FSH. The use of these in amenorrhœa is suggested, but clinical results do not warrant this application. All the gonadotropins are orally inactive.

There is some evidence that prolactin, the lactogenic principle of the anterior pituitary does enhance lactation. Its general use up to the present has been limited by certain practical difficulties attending its administration, especially pain at the site of injection.

Several œstrogens are available in pure form. These are œstrone, œstriol and œstradiol. In addition to these there are the esters of œstradiol, the benzoate and the dipropionate. As their names imply, these are all able to produce signs of œstrus-desquamation of the cornified cells of the vaginal mucosa. While their physiological action is qualitatively identical, they vary greatly in the duration and intensity of their effect.

That œstrogens are essential for a proper progestational effect is suggested by their high concentration in the blood during ovulation: indeed, progestogen cannot effect its characteristic endometrial response without preliminary priming by œstrogen. It is on this basis that œstrogens are used in sterility. In a similar

TABLE I.

CLASSIFICATION, NOMENCLATURE AND STANDARDIZATION

Accepted name	*Description*	*Source*	*I.U. per mg.*	*Comments on activity*
Pituitary gonadotropins	Impure extracts.	Anterior pituitary cattle.	10	Contain both follicle stimulating and luteinizing substances (FSH and LH).
Chorionic gonadotropins:				
1. Human	(*a*) Placental extracts APL.	Human placentæ.	10	Mostly LH some FSH.
	(*b*) Pregnancy urine APL.		10	Mostly LH some FSH.
	(*c*) Menopausal urine.			Mostly FSH some LH.
2. Equine	Pregnant mare serum.	Pregnant mares.	4	Mostly FSH.
Prolactin	Relatively pure extract.	Anterior pituitary cattle.	10	Effective in milk secretion after priming by ovary.
Androgens:				
1. Androsterone	Excretory product of male hormone testosterone.	Synthetic and male urine.	10	
2. Dehydroandrosterone	Intermediate product in metabolism of testosterone.	Synthetic and male urine.	10	
3. Anhydro-iso androsterone	Closely related to sex steroids.	Adrenal cortex.		
4. Testosterone	True hormone of testis.	Male urine and synthetic from cholesterol.	50	Esterification with propionic acid increases intensity of action 7 times and duration of action 2 times.
T propionate	Propionic acid ester of testosterone.	Synthetic.		
Methyl testosterone	Methyl derivative.	Synthetic.		Especially useful orally.
Œstrogens:				
1. Œstrone (Theelin)	Excretory product of *a*-œstradiol.	Urine.	10,000	
2. Œstriol (Theelol)	Excretory product of *a*-œstradiol.	Pregnancy urine and placentæ.		Effective orally only.
3. *a*-œstradiol	True follicular hormone.	Ovary and pregnant urine.		Œstrone and the esters of *a*-œstradiol cannot be compared properly on basis of I.U. Intensity increased on esterification. *Duration of action—œstrone 4 days, œstradiol 17, benzoate 14, dipropionate 42 days.*
Benzoate	Monobenzoate of *a*-œstradiol.	Synthetic.	10,000	
Dipropionate	Dipropionate of *a*-œstradiol.	Synthetic.	10,000	
Progestogens:				
1. Progesterone	True corpus luteum hormone.	From C.L. and synthetic from stigmasterol.	1	Effective only after œstrogen priming.
2. Pregneninolone	Anhydro-hydroxy-progesterone.	Synthetic.	0.25	Effective orally.

manner prolactin cannot produce lactation until the acini and ducts of the mammary gland are primed by the required amounts of œstrogen and progestogen in that order. Too great a quantity of either may inhibit lactation, thus providing a rationale for the use of large quantities of œstrogen in suppressing that phenomenon. Since œstrogens are essential for the growth and activity of the genital tract, and since they stimulate the epithelium here, producing thickening and hyperæmia, they have been used extensively in vulvovaginitis, kraurosis, leukoplakia and genital hypoplasia associated with amenorrhœa, sterility and menopausal changes.

Progestogens prepare the endometrium for nidation of the ovum and are responsible for the formation of the decidua. They inhibit menstruation and are valuable in functional bleeding. Progesterone is the common member of this group. Used in adequate amounts, it is of incalculable value in habitual and threatened abortion, and in premature labour, providing these complications have an endocrine basis. Progesterone controls the metabolism of œstradiol. In the presence of a functioning endometrium, progesterone effects the change from œstradiol and œstrone to the inactive excretory form œstriol.

This paper is not concerned with the effect of androgens in the male. In the female, contrary to common belief, androgens do not neutalize the effects of œstrogens. It would be more correct to say that œstradiol and testosterone exert a co-operative synergistic effect in the female genital tract when the dosage is regu-

TABLE II.

SOME EFFECTS OF PURE SEX HORMONES TO INDICATE THEIR POTENTIALLY BISEXUAL ACTION IN HUMAN BEINGS

		No œstrone priming	
	Œstrone	*Progesterone*	*Testosterone*
Uterus:			
Endometrium	Proliferative.	Slight proliferation.	Progestational.
Myometrium	Marked growth and hypertrophy.	Moderate growth.	Quite marked growth.
Rhythmic motility	Induces.	Decreases.	Decreases.
Vaginal mucosa	Growth, proliferation stratification and mucification.	Minimal proliferation marked mucification.	Growth, proliferation but only slight mucification.
Breast	Duct proliferation.	Mild proliferation.	Duct proliferation and lobular growth.
	Initial priming with œstrone		
Uterus:			
Endometrium	Proliferative.	Proliferation and progestive changes.	Proliferation and progestive changes.
Myometrial growth	As above.	Moderate effect.	Very marked growth.
Rhythmic motility		Inhibited.	Inhibited.
Vaginal mucosa		Mucification.	Marked mucification.
Menstruation	Inhibited.	Inhibited?	Inhibited.
Ovulation		Inhibited.	Inhibited.
Pregnancy (delivery)	Hastens.	Prolongs.	Prolongs.
Lactation	Inhibited unless nursing.	No effect?	Inhibits unless nursing.

TABLE III.

COMPARING THE ACTIVITY OF ONE MILLIGRAM (10,000 I.U.) OF THE ŒSTROGENS IN COMMON USE

Substance	*Vehicle*	*Route*	*Mouse U*	*Rat unit*	*Duration of physiological effect of 50 γ in rat*	*Human dose equivalent for one month intramuscularly*	
						Amount	*Doses*
Œstrone	oil	parenteral	5,000	1,000	4 days	30 to 35 mg.	12
Œstrone	water	parenteral	10,000	2,000	2 days	60 to 70 mg.	18
Œstrone	oil	peroral	800	50			
Œstrone	water	peroral	1,500	100			
a-Œstradiol	oil	parenteral	15,000	8,000	7 days	26 mg.	8
Œstradiol benzoate	oil	parenteral	15,000	10,000	14 days	8 mg.	4
Œstradiol dipropionate	oil	parenteral	22,000	18,000	42 days	4 mg.	2

Œstradiol and its esters, given orally, require about five to ten times the intramuscular dose.

lated. Like progesterone, the male sex hormone modifies the action of œstradiol and effects its increased metabolism, resulting in an increased excretion of œstriol. Thus it inhibits the rhythmic intermittent uterine contractions, decreasing the blood supply to the uterus. It also stimulates the myometrial elements, causing constriction of the spiral arterioles, thus reducing the blood flow to the endometrium. For this reason testosterone is extremely useful in the immediate treatment of uterine bleeding, no matter what the cause. It is almost of equal value in dysmenorrhœa and some forms of mastodynia. Table II illustrates some of the properties of the sex sterols.

Selection of preparations and route of administration.

Gonadotropins.—So long as these are fresh,

TABLE IV.

EXCRETION OF SEX HORMONES IN VARIOUS CONDITIONS

Condition	*Gonadotropins R.U. for 24 hours*	*Androgens mg. for 24 hours*	*Total γ for 24 hours*	*Œstrogens* — *Percentage of total for 24 hours*			*Progesterone*	*Comments*
				Œstrone	*Œstradiol*	*Œstriol*	*Pregnandiol mg. for 24 hrs.*	
Prepubertal female	1 to 4	small am'ts	1 to 9	..	100.0	..	none	Conversion and inactivation of œstradiol and œstrone to œstriol depends on production of progesterone and intact endometrium.
Adult female cycle		3 to 4						
day 1 to 7	2 to 10		1 to 6	..	..	..	..	
8 to 12	7 to 15		6 to 9	50.0	20.0	30.0	none?	
13 to 15	50 to 100		10 to 25	..	..	..	2 to 4	
16 to 18	17 to 7		40 to 60	20.0	10.0	70.0	16	
19 to 27	5 to 2		4 to 25	60.0	4.0	36.0	28	
28	2		25	..	100.0	..	2 to 4	
Amenorrhœa and oligomenorrhœa (ovarian)	increased	2 to 4	very low without peaks				low or none	
Amenorrhœa (pituitary)	decreased	4 to 12	very low				none	
Meno-metrorrhagia	variable	low	60 to 140	..	100.0	..	very low	
Menopause cycling	5 to 25	3 to 6	low with small peaks				low	
Irregular or no cycling	decreased	4 to 8	very low				none	
Castrate	increased	2 to 10	none?				none	
Pregnancy:								
Days 0 to 20	25 to 20,000	....	50 to 200	30.0	10.0	60.0	5 to 15	Stability of pregnancy depends on adequate production of progesterone by corpus luteum for first 3 months and by the placenta for the remainder of term.
21 to 60	100,000 to 500,000	5 to 15	200 to 800	7.0	3.0	90.0	35 to 85	
61 to 120	10,000 or less	....	800 to 10,000	0.25	0.05	99.7	85 to 95	
121 to 275	3,000 or less	....	10,000 to 30,000	0.15	0.01	99.8	75 to 80	
Term	200 to 300	4 to 7	500 to 1,000	..	40.0	60.0	2 to 5	
After delivery	5 to 25	2 to 4	10 to 25	..	100.0	..	2	
Threatened abortion:								Faulty placental activation.
Early 2 to 3	25 to 5,000	....	2,000 to 4,000	15.0	45.0	40.0	5 to 15	
Late 8 to 9	5,000 to 10,000	....	3,000 to 5,000	..	40.0	60.0	12 to 17	Early placental degeneration.
Prepubertal male	1 to 2	small am'ts	?				..	
Adult males	3 to 7	6 to 8	9 to 12				..	
Eunochoids, castrates	increased	0 to 2	1 to 3				..	
Hirsute women	3 to 15	5 to 30	6 to 30				..	
Basophilism:								
1. Pituitary	increased	25 to 300	variable				..	Mainly androsterone.
2. Adrenal	variable	150 to 175	1 to 4				..	70 per cent Δ dehydroandrosterone.
Hydatid mole	Up to 100 X pregnant							
Granulosa cell tumour	....	....	300 to 600				..	Mainly œstrone.
Arrhenoblastoma	....	5 to 8	low				..	Δ Dehydroandrosterone.
Acromegaly	increased	0.1 to 0.8	2 to 3				..	
Metropathia hæmorrhagica	variable	low	low	no peaks			none	Not true menses.

assayed by standard procedures, and produced by a reliable manufacturer, they may be used where indicated and the stated claims for potency accepted. One must bear in mind however that many of these solutions deteriorate on standing and all of them are inactive orally. Given intramuscularly or intravenously they are active, but precautions against anaphylactic reactions should be taken, since most of them contain protein or are themselves protein in nature. One should recall also, that preparations derived from mare serum and menopausal urine are essentially FSH in content, whereas pregnancy urine preparations are mainly LH, and their effects differ.

Progestogens.—Extracts of the corpus luteum, while less expensive, are also less active than progesterone. The oral preparation, pregneninolone, given by mouth has about one-quarter the activity weight for weight of progesterone intramuscularly.

Androgens.—The effect of testosterone is intensified and prolonged by esterification. Testosterone propionate is the most potent androgenic substance known. Measured by its effect on the seminal vesicles it is seven times as potent as testosterone and its effect lasts twice as long. It can be used orally, intramuscularly, or by inunction, but it is more economical to use the methyl derivative for oral administration.

Œstrogens.—Œstrone, or theelin, as it is frequently called is the most commonly used œstrogen. This is unfortunate, since compared with the others it is quite inefficient. Its solubility in oil is very low, so that high concentrations are not available. It is absorbed rapidly and excreted with equal ease, so that its duration of action is very short. Œstradiol is the form of the hormone which exists in the ovary. It may be used orally, intramuscularly, by inunction or in the form of vaginal suppositories. Œstriol is an excretory product of œstradiol. It is active orally, but valueless by the intramuscular route.

Esterification of œstradiol to form the benzoate or the dipropionate increases its solubility in oil so that large amounts can be administered in small injections. It also enhances the intensity of its action and increases the duration of its effect. There is no special advantage in using the esters of œstradiol for oral purposes or in the form of vaginal suppositories. The chief advantage offered by esterification is in the intramuscular routine and inunction. With the dipropionate adequate therapy can be given with a longer interval between treatments, making it especially useful in those cases where therapy must continue over a long time.

Table III attempts a comparison in activity of some of the œstrogens by different routes. This comparison in terms of relative potency is difficult. Qualitatively, the action of œstrone, œstradiol, œstradiol benzoate and œstradiol dipropionate is the same. Quantitatively, as tested in the female castrate rat, 0.05 mg. œstrone gives a vaginal response lasting 4 days, the œstradiol effect lasts 7 days, œstradiol benzoate is effective for 14 days while the œstradiol dipropionate response lasts 42 days. Since these amounts represent the same number of international units, it shows in a striking manner that prescribing by international units is misleading. Rat units, mouse units and international units are concerned only with the immediate effect of a minimal dose and ignore completely duration and intensity of action. From what has been said it seems clear that œstradiol diproprionate is the most economical as well as the most effective œstrogen known at the present time, since it provides effective therapy with the least inconvenience to the patient's comfort.

We have used the sex sterols by two other routes. We have found that the subcutaneous implantation of pellets was followed by excellent results for periods varying from three to six months, depending on the weight and size of the pellet. More recently, we have treated some patients with a solution of the material in propylene glycol administered by dropper under the tongue. The sex sterols are rapidly absorbed from this region and preliminary findings lead us to suggest that this route may be the most practical and the most economical.

We have heard so many complaints about skin reactions from the intramuscular injections that it seems well to describe the method we use. Induration of the skin usually follows the too superficial injection of the oily material. Our practice has been to dry sterilize a two c.c. syringe together with a 1½ inch 18 gauge needle and a 2½ inch 23 gauge needle, the latter having a long bevel. The ampoule is warmed to about 50° C., and opened after cleasing the neck of the vial and file with alcohol. The material is removed through the 18 gauge needle. This needle is then removed and the 23 gauge needle applied. In this way there is no material on the outside of the needle by which the injection

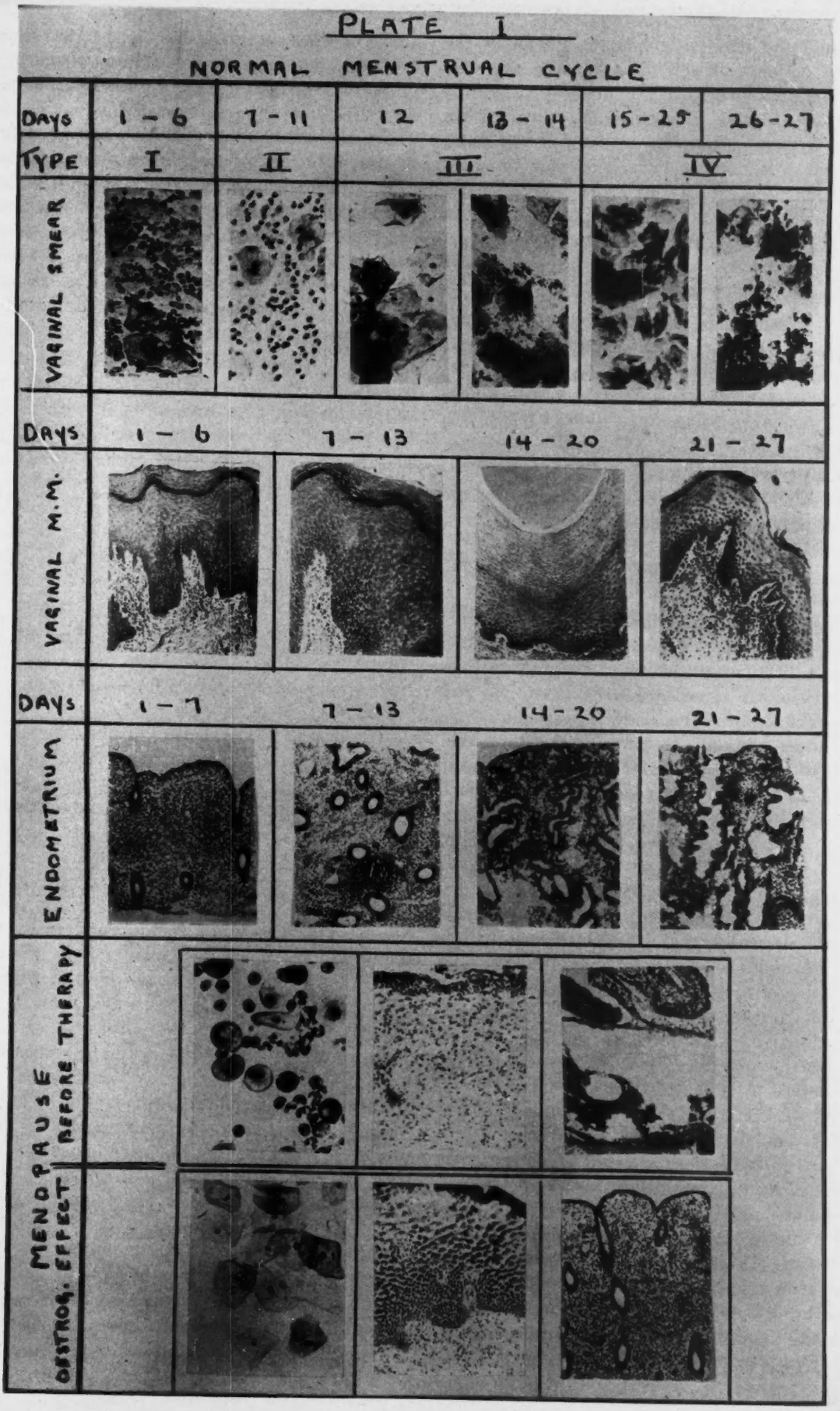
PLATE I
NORMAL MENSTRUAL CYCLE
DAYS
1 - 6
7 - 11
12
13 - 14
15 - 25
26 - 27
TYPE
I
II
III
IV
VAGINAL SMEAR
DAYS
1 - 6
7 - 13
14 - 20
21 - 27
VAGINAL M.M.
DAYS
1 - 7
7 - 13
14 - 20
21 - 27
ENDOMETRIUM
MENOPAUSE
BEFORE THERAPY
DESTROY. EFFECT

is made, and none is left in the tissues as the needle enters. Injections are made into the upper and outer quadrant of the gluteal region, ether being used to cleanse the skin. With these precautions and by alternating the sides for each injection we have been able to avoid any induration at the site. The syringe and needles are then cleansed by immersing in a bath of carbon tetrachloride. On removal from this, they usually drain dry and are ready for sterilizing without further cleansing.

CLINICAL CONSIDERATIONS

It is a common fashion nowadays to consider every obscure condition endocrine in origin, so that frequently no attempt is made to exclude a non-endocrine basis. This is so because too great emphasis has been placed on information obtained from hormone assays, and because there is too much confusing evidence regarding the therapeutic value of the sex hormones in a variety of unrelated conditions.

The great value of the pregnancy tests (for chorionic gonadotropins) is in the diagnosis of chorionepithelioma and in detecting its recurrence. In normal pregnancy their only value is in confirming suspicions rather earlier than ordinary. Our experience with œstrogenic and androgenic assays leads us to suggest that these procedures are still in the realm of research. They do provide confirmatory information, but normal values vary so widely and estimations in any individual case must be made so frequently and over a period of at least a month, that they become impractical. Progesterone is not found in the urine as such. Its excretory product, pregnandiol, is found in too small amounts normally to give anything but qualitative information. In pregnancy, the periodic estimation of pregnandiol excretion does provide valuable information with regard to corpus luteum activity and placental function. Its use as a test for pregnancy in our experience is not as practical as is the test for chorionic gonadotropin. There is one exception to these general remarks and that is in the case of basophilism. The excretion of specific types of androgen is of value in differentiating between pituitary and adrenal basophilism. In the latter, transdehydroandrosterone is excreted in rather large quantities. This is not found in any other condition with the exception of arrhenoblastoma of the ovary, and then only small amounts are excreted. The excretion of sex hormones in a variety of disorders is classified in Table IV.

There are now available to us two simple diagnostic methods for determining the activity of the ovaries. The first of these, endometrial suction biopsy is a well established procedure. The exact technique may be found in any recent treatise in gyæcology. The test yields information with regard to endometrial proliferation and secretion, determines the phase of the cycle, and, by inference, the secretory activity of the ovary. Preparation and interpretation of the sections require the assistance of a pathologist so that the general use of this method is limited.

The second method, and much the simpler, is the study of the vaginal smear. A clean specimen is collected from the hollowed valve of the vaginal speculum by drawing it up with a little water in a medicine dropper. Several thin smears are made on glass slides, dried and stained with acid fuchsin for one minute, and washed with tap water. The smears are now examined. Plate I illustrates the normal menstrual changes and the appearance in some ovarian disorders. The whole procedure can be carried out in a few minutes and offers a useful aid in diagnosis and a means of evaluating the results of therapy.

Disorders of the menarche.—Menstrual disorders may have an organic, nervous or endocrine basis. General debilitating diseases are common causes of amenorrhœa; local uterine lesions may give rise to excessive bleeding. Emotional disturbances, environmental changes and similar disorders often lead to amenorrhœa. These causes should be excluded before endocrine therapy is attempted. Faulty nutrition and mild hypothyroid states are overlooked too often as etiological factors, and many patients will be relieved of symptoms by dietary correction in addition to small doses of thyroid extract. Ovarian hypoplasia may be due to inefficient stimulus from the pituitary, or to a failure on the part of the ovary to respond to normal amounts of gonadotropic hormones. In such cases there is inadequate secretion of œstradiol, with resultant uterine hypoplasia. The uterus may fail to react to normal ovarian secretion (uterine refractivity). In all these cases the uterus is small, the endometrium atrophic, and the flow reduced, absent, or the interval lengthened. In other cases ovulation may fail to occur. The ovaries are filled with multiple cysts and there is complete absence of corpus luteum formation. Here the follicular hormone, œstradiol, is present in excessive amount but

progesterone is absent or deficient. This results in irregularities of menstruation, profuse bleeding or mild continuous hæmorrhage alternating with periods of amenorrhœa.

Amenorrhœa, hypomenorrhœa and oligomenorrhœa.—Treatment is directed first towards replacement therapy to build up the uterus to adult size. This is accomplished by giving large doses of œstrogens supplemented with progesterone during the second half of the cycle. Our routine is as follows: (1) Thyroid extract to tolerance regardless of the initial basal metabolic rate unless it is increased beyond +20. (2) Œstradiol dipropionate (di-ovocylin) and progesterone (lutocylin) cyclically

Day	1	5	9	13	17	21	25
Di-ovocylin mg.	1.0	2.5	2.5	5.0	5.0	2.5	1
Lutocylin mg. .	0	0	0	0	5.0	10.0	5

With this routine typical menstrual bleeding may be expected about the 28th to 30th day. This procedure is repeated until two or three periods are produced. In most cases of secondary amenorrhœa normal menstruation proceeds thereafter. Some cases do relapse and the course should then be repeated. Oligomenorrhœa and hypomenorrhœa respond more favourably and with less difficulty.

The primary type of amenorrhœa is more resistant to this routine, and it is doubtful whether such a procedure is even rational in this case, since the bleeding produced is entirely artificial. It should be added that in all these disturbances, in the absence of demonstrable constitutional disease and of any desire for pregnancy, there is no indication for attempts at treatment beyond the possible giving of thyroid and correcting any dietary failing.

If the uterine hypoplasia is due to defective ovarian secretion the treatment is far less satisfactory. Gonadotropic hormones of various origin may be tried. On a theoretical basis the FSH factor should be given for the first two weeks and the LH factor for the following two. Our experience has shown this procedure to be disappointing. It is true that ovulation can be produced by a single intravenous administration of mare serum gonadotropins, using from 40 to 80 RU as a dose, but this single stimulus is quite insufficient to start a cycle. The dangers of serum sickness and anaphylactic shock need to be reckoned with unless great caution is practised. It is our belief that these preparations are occasionally useful if fresh material is available and adequate amounts are used.

We are not of course oblivious of the beneficial effect of small doses of x-ray to the ovaries, the rationale being to inactivate the ovaries for a short time, in the hope that the return of function will be exaggerated to the point of normalcy.

Menorrhagia, metrorrhagia, metropathia hæmorrhagica.—Functional irregularities in uterine bleeding are due to disturbances in the physiological reciprocities of the ovaries and uterus. Treatment should be directed toward the primary cause. The immediate use of surgery, radium or x-ray is an admission of defeat of specific endocrine therapy. The cause of bleeding which comes from an excessively proliferated endometrium is not completely understood and the theories advanced do not fall within the scope of the present discussion. Gonadotropins have been tried extensively with the hope of producing supernumerary corpora lutea. This is a dangerous procedure and may only intensify the bleeding by first increasing the œstrogenic output which is already great. There is no rationale for massive dosage œstrogen therapy, such a practice is indeed dangerous, especially during the period of bleeding.

Two procedures have proved valuable in our hands. The first of these is the use of progesterone. This substance counteracts excessive œstrogen production and transforms the hyperproliferated endometrium into a secretory one. Four intramuscular injections of 5 to 10 mg. are given on alternate days every 20 days, thus producing a period every 28 days. If symptoms are not severe as little as 2 mg. may be sufficient. Where supplementary medication is required, pregneninolone, 5 mg. daily, orally, is useful. Many cases do not respond to this therapy and in these we have recourse to testosterone propionate, giving 10 to 25 mg. daily or twice daily for two consecutive days, the first dose being administered on the second or third day of bleeding. Hæmorrhage is controlled in from 12 to 24 hours after the first injection. Supportive treatment during the cycle with small doses of methyl-testosterone orally in the second half of the interval is a useful measure in preventing recurrences. It is our firm belief that the most useful material in the treatment of uterine bleeding, no matter what the cause, is testosterone propionate. It is important to mention in this regard that very frequently in about 12 to 24 hours after the bleeding has been controlled, the patient experiences "flooding". This lasts about

TABLE V.

SYNOPTIC GUIDE TO DIAGNOSIS AND TREATMENT

CONDITION	ENDOCRINE BASIS	CLINICAL DIAGNOSIS Symptons and Signs	CLINICAL AIDS Laboratory Findings	TREATMENT	RATIONALE FOR TREATMENT	RESULTS	COMMENTS
Menstrual disorders: (Amenorrhœa, hypo. and oligomenorrhœa): 1. Pregnancy.	Active corpus luteum.	Progressive uterine enlargement.	Positive Ascheim-Zondek. Increase œstrogen, pregnandiol.	None	.....	.....	.....
2. Pituitary type.	Pituitary hypofunction (atrophy or destruction) with ineffective stimulation to ovaries.	Genital hypoplasia, retarded skeletal growth, girdlemons-mammary obesity, sterility and frigidity.	Reduced prolan and œstrone excretion, high glucose tolerance.	Adequate diet, gonadotropins 500 R.U. 3 X weekly, thyroid extract. Stim. dose x-ray to pituitary and ovary.	Replacement therapy. Stimulated with x-ray causes initial inactivity then overactivity.	Unsatisfactory or temporary improvement, better effects in adolescence than after 30.	Guard against serum sickness with use of material from pregnant mare serum.
3. Pituitary-thyroid type.	Above with hypothyroidism.	Above with inactivity, dry skin, mental torpor.	Above plus low basal metabolic rate.	Thyroid in full tolerated dose together with above régime.	As above.	Good where hypothyroidism is a large factor.	.....
4. Ovarian type.	Inadequate ovarian secretion.	Sterility, loss of libido, occasionally genital hypoplasia, span exceeds height, trochanteric fat.	Excess urinary gonadotropin, decreased œstrogen excretion, atrophic endometrium (biopsy) vaginal smear type I or II.	Thyroid extract. Œstradiol dipropionate and progesterone cyclically for at least three cycles.	Replacement therapy to build up hypoplastic uterus to adult size.	Quite good except in primary amenorrhœa which regresses occasionally and requires several courses.	.....
5. Uterine type.	Uterine refractivity or hypoplasia.	Uterus small, underdeveloped.	Endometrium atrophic, œstrogen excretion normal, no pregnandiol. Smear I or II.	As above.	As above.	As above.	.....
(Excessive menstrual or intermenstrual bleeding): 1. Pituitary type (menorrhagia).	Pituitary basophil hyperactive with resulting persistence of Graafian follicles and no corpus luteum formed.	Prepubertal and pubertal form with associated genital hypertrophy or menopausal form seen as part of the menopausal syndrome.	Increased excretion of F.S.H. and œstrogens. Pregnandiol decreased or absent. Hyperplastic endometrium, no secretory phase. Smear type III.	1. Pituitary gonadotropins 40 to 80 R.U. intravenously. 2. Progesterone 5 to 10 mg. given intramuscularly on alternate days for 4 doses every 20 days, or pregneninolone orally 5 mg. t.i.d. for 8 days every 16 days.	To cause ovulation with resulting corpus luteum and secretory phase. To interrupt bleeding by producing a secretory phase, thus inducing rhythmicity.	Occasionally useful. Results good if symptoms not too severe or of too long duration.	Occasionally increase the bleeding. If no response treat as metropathia hæmorrhagica.
2. Ovarian (Metrorrhagia and metropathia hæmorrhagica).	Rhythmic activity of the ovaries lost, corpus luteum phase absent resulting in continuous œstrinism.	Persistent follicle cysts, no corpus luteum formed, amenorrhœa followed by continuous bleeding (not true menstruation). Usually no dysmenorrhœa.	Œstrogens diminished but constant, no pregnandiol endometrium thickened and of "Swiss cheese" type, and no secretory phase.	Testosterone propionate 10 to 25 mg. intramuscularly daily or twice daily for two days every 24 days, or Methyltestosterone orally 5 mg. t.i.d. for 2 days every 24 days.	Inhibits rhythmic activity of myometrium, constricts spiral arterioles and reduces blood flow to endometrium.	Bleeding usually controlled in 12 to 24 hours. Best single agent available.	Long continued use may produce hypoplastic uterus, but no danger with this dosage.
Dysmenorrhœa (Menstrual tension).	Myometrial hyperactivity from oversecretion of œstrogen or unopposed action of normal secretion.	Pain before or during menstruation or both.	Usually not out of the ordinary findings.	Testosterone propionate 5 to 10 mg. daily or on alternate days from one day previous to usual onset of symptoms for 2 to 4 doses.	Androgen deficiency leads to unopposed œstrogen action.	Excellent.	Treatment may cause delay or suppression of period immediately following but this no special concern.
Menopause.	Endocrine imbalance associated with change from sexual activity to sexual inactivity.	Menorrhagia followed by amenorrhœa, hot flushes, vertigo, faintness, obesity. Hyperthyroidism followed by hypothyroidism. Pruritus vulvæ, alkaline vaginal secretion, psychic changes.	High œstrogens excretion, absent pregnandiol, then low œstrogen with increased gonadotropins. Hyperplastic endometrium changing to hypoplastic and typical vaginal smear.	1. *No menorrhagia*—œstradiol dipropionate 5 mg. weekly for 3 to 4 weeks then maintain on smaller dosage with increased intervals (1 mg. 14 to 21 days). Or orally—œstradiol 5 mg. daily and reduce as above. 2. Where menorrhagia a factor, testos. propionate 10 to 25 mg. weekly and reduce dose and lengthen interval when symptoms controlled or change to methyl-testosterone orally.	Replacement therapy with gradual withdrawal. Depression of all ovarian activity.	Effect in 24 hours. Vaginal smear changes from I to IV in 4 to 6 days, acid secretion. Normal menses may or may not continue. Bleeding contolled and good symptomatic relief.	Euphoria very common but must not influence continuation of treatment—judge by vaginal smear only. Use only where œstrogens ineffective and where bleeding is prominent.

Vaginitis. Vulvovaginitis (gonococcal).	Withdrawal of maternal œstrogen effect reduces thickness of vag. mucosa and changes secretion from acid to alkaline rendering it vulnerable to infection.	Red congested mucosa with small erosions and a scant alkaline secretion.	Vaginal smear type I or II. Neisserian organisms. Alkaline reaction.	Œstradiol dipropionate 2 mg. at 4 day intervals for 6 doses, then at 7 to 10 day intervals for 6 weeks. Vag. supposit. of 0.4 mg. each night for 7 to 10 days and alternate nights for 50 days.	To increase thickness of vag. mucosa, cause epithelization and produce acid secretion.	Quite good if no other focus of infection outside sphere of action of œstrogens.	Treatment must be maintained until clinical and bacterial cure. Follow effect by vag. smear.
Senile vaginitis.	Œstrogen deficiency.	Atrophic vaginal mucosa.	Low œstrogen excretion, atrophic vag. mucosa, smear type I, nearly all leucocytes.	Œstrad. dipropionate 2.5 to 5 mg. at weekly intervals and suppositories 0.4 mg. on alternate nights for 4 weeks, then suppositories of reduced strength every 3 to 4 nights to maintain physiological state.	As in case of vaginitis of Neisserian origin.	Usually complete relief in 4 weeks. Type IV smear should be obtained in 7 to 10 days.	Follow effect by vag. smear to be certain that results are maintained.
Pruritus vulvæ. Menopausal type.	As under menopause.	Part of menopause syndrome.	As in menopause.	As for menopause using œstradiol-dipropionate with the addition of suppositories as a supportive measure and or local inunction of œstradiol ointment.	Replacement therapy to increase thickness of mucosa, cause epithelization and produce an acid secretion.	Usually very good response within 4 to 6 days.	Supportive treatment should be continued for several weeks.
Kraurosis vulvæ.	Œstrogen deficiency.	Occurs 10 to 15 years after menopause associated with atrophy of labia and return of vag. mucosa to infantile state. Associated kraurotic changes.	As in menopause.	Intense intramuscular therapy with œstrad. diprop. 5 to 10 mg. twice weekly, suppositories each night and inunction of labia. Routine to continue for 3 to 4 months and course repeated in 6 to 8 months.	As above.	Healing of the kraurotic lesions and relief of symptoms is the most dramatic effect.	Bleeding may occur but should occasion no concern—it will disappear when intense therapy is reduced.
Cystic disease of breast. 1. Lobular.	Primary hypo-ovarianism with increased activity of pituitary to compensate.	Lobular hyperplasia with non-encapsulated nodules and minute cysts, arising from prolif. of epithelial cells of terminal ducts and acini. Occasional nipple bleeding. (Mazer's 1st type).	As in hypo-ovarianism.	Œstrad. diprop. and progesterone during the second half of cycle or œstradiol dipropionate 1 to 2.5 mg. weekly or twice a week in the mid interval. The second procedure is one of choice unless excessive bleeding follows.	Replacement therapy.	Results fairly good in most cases.	Relief after one course for 2 to 3 months then regression requires further treatment.
2. Cystic hyperplasia; mastodynia.	Hypersecretion of œst. by cystic ovaries resulting in continuous proliferation without secretory phase.	Well circumscribed cysts in centre of breast. (Mazer's type II.) Associated with follicular cysts of the ovaries.	Increased œstrogens excreted. Hyperplastic endometrium with no secretory phase. Vag. smear type III.	Testosterone propionate 25 mg. b.i.d. for 2 to 3 days or once daily.	Suppression of œstrogen activity.	Complete symptomatic relief with usually no recurrence.	Period immediately following may be delayed or absent, or of short duration.
Pregnancy: Nausea and vomiting.	No real endocrine basis.			None.	None.	None.	
Threatened abortion.	Progesterone deficiency due probably to placental inefficiency.	Pain, cramps, bloody discharge—menstrual in type without dilatation of os usually about 3rd month.	Disturbance of œstrogen metabolism. Decreased pregnandiol. Excess œstrone over œstriol.	Progesterone 5 to 10 mg. daily or b.i.d. with pregneninolone 5 mg. t.i.d. orally as supportive measure until bleeding stopped, then for 3 to 4 days at periods.	Replacement therapy for inadequate production by placenta to help stabilize pregnancy.	Good if treatment started early along with usual measures.	No value if os is dilated.
Habitual abortion.	Progesterone deficiency if no constitutional cause or blighted ova.	As above.	As above.	As above but should be given routinely at calculated period in anticipation of any complication.	As above.	Good if started early and no anatomical defect such as blighted ova in the etiology.	No value if os is dilated.
Premature labour.	Progesterone deficiency.	Hæmorrhage, rhythmic pains, moderate dilatation of os, etc.	Rise in gonadotropins, excess œstrone over œstriol due to progesterone def. from early degenerative changes in placenta.	Progesterone 10 mg. or more daily or twice daily.	To offset action of œstrone on uterus and control contractions.	Depend on early recognition of symptoms and adequate treatment.	No value if os dilated and membranes bulge.

15 minutes and the patient should be warned, so that embarrassment may be avoided.

Dysmenorrhœa.—The etiology of this condition is still obscure. Most investigators feel that it is due to increased myometrial activity consequent to hyperœstrinism. The most effective remedy is found in the androgens. This is not entirely empirical, since it is now well established that the androgens do play a definite rôle in the cyclical phenomena of menstruation. The suggested possibility that androgen deficiency leads to unopposed œstrogen action and dysmenorrhœa provides the rationale for its use here. Testosterone propionate, 5 to 10 mg., depending on the gravity of the symptoms, is given on alternate days with the first dose on the day previous to the usual time of onset, the treatment being continued through the period during which symptoms are usually present. The next following period of bleeding may be delayed, scanty or absent, but need occasion no concern. In several cases we have suppressed completely several consecutive periods, and found that, with the cessation of treatment, subsequent cycles were symptomless.

Much has been said and written about the dangers of producing hirsutism by this medication. We have used up to 300 mg. per month over a period of three months in several cases without any evidence of masculinization. The threshold for producing such an effect is about 500 mg. a month, an amount far beyond that of therapeutic necessity. Should hirsuties appear, or hoarseness, the patient may be assured that these will disappear entirely after the treatment is stopped.

The menopause syndrome.—The clinical manifestations in this condition and their intensity vary with the degree of œstrogen deficiency. Whether the autonomic imbalance, identified with hot flushes, is or is not part of the same deficiency is still in doubt. Where menorrhagia is not a prominent factor we administer œstrogens by the intramuscular route, using the long acting œstradiol dipropionate (di-ovocylin) to restore the normal hormonal equilibrium and compensate for the abrupt or gradual withdrawal of the ovarian secretion. Patients with severe symptoms are given 5 mg. at weekly intervals for three to four weeks. They are then maintained on smaller doses, 1 to 2 mg. at weekly or ten day intervals. Some whose symptoms are less severe can be controlled with as little as 1 mg. at 14 to 21 day intervals. The therapy is continued until the interval between injections can be lengthened to one month without return of symptoms. In appraising the results it is well to recall that the subjective is a prominent factor in the complaints and too great emphasis must not be put on the patient's evaluation of the treatment. Frequent vaginal smears are of great assistance in judging the value of this routine. Symptoms disappear very rapidly, often within 24 hours. The vaginal smear changes from round or oval epithelial cells and leucocytes to large squamous epithelial cells associated with normal activity in about four to six days after the first injection (Plate I).

Occasionally patients are encountered who do not respond to œstrogens no matter how large the dose. If there is no clinical improvement in two or three weeks by the criteria mentioned, it is useless to persist with œstrogens. In these, as in cases where menorrhagia is a prominent factor, we have used androgens with good results. Testosterone propionate in doses of 10 to 25 mg. at weekly intervals is administered until the symptoms are controlled when the dose is decreased and the time interval lengthened.

Disorders affecting the vaginal epithelium.

Vulvovaginitis.—Infections of the immature vagina are ordinarily very difficult to handle. The differentiation of specific and transmissible forms (gonococcic) from non-specific types is difficult and outside the scope of this paper. The mucosa is red, congested and eroded. The secretions are alkaline. In the newborn, under the influence of maternal œstrogens, the mucosa is thick, the secretions are acid and the flora bacillary in type. Within three weeks or a month after birth the mucosa becomes thin and the secretions alkaline and scant. It remains in this vulnerable state until puberty when the œstrogens again convert it to the thickened form. After the menopause, the mucosa again reverts to the pre-pubertal state and again becomes liable to infection and trauma.

The treatment of vulvovaginitis with œstrogens is an attempt to promote epithelization of the mucosa and produce an acid secretion. Œstradiol dipropionate (di-ovocylin), 2 mg. at 4 day intervals is given for six doses and then decreased to weekly or ten-day intervals for another month or six weeks. Vaginal suppositories containing 0.4 mg. are inserted nightly for a week or ten days and then on alternate nights until a clinical and bacteriological cure is effected. If the treatment has been adequate

there should be no recurrence at the end of one month after the last dose has been administered. Recurrences after three months are certainly due to reinfection.

Senile vaginitis, pruritus vulvæ and kraurosis.—The atrophic mucosa and leucocytic smear in these cases is taken as evidence of extreme œstrogen deficiency. To increase the thickness of the epithelium we use di-ovocylin, 2.5 to 5.0 mg., at weekly intervals together with suppositories (0.4 mg.) on alternate nights, for about 4 weeks. After this, vaginal suppositories of reduced strength twice a week will maintain the physiological state. Regression is unusual and can be treated with a further intramuscular course.

Pruritus associated with the menopause is relieved by the treatment already outlined for that syndrome if vaginal suppositories are used as a supportive part of that regimen. Pruritus which arises about 10 to 15 years after the menopause and which is associated with labial atrophy and kraurotic changes in the vaginal mucosa requires intensive treatment. In addition to the ordinary measures as outlined for senile vaginitis, we have found that the local application of an inunction containing 1.0 mg. œstradiol dipropionate per gram of adeps lanæ is a useful adjunct for at least three or four months and the course repeated after an interval of four to six months to prevent regression and ensure freedom from symptoms.

Cystic disease of the breast.—(1) *Lobular type.*—This is a painful hyperplasia of the terminal ducts and acini of the breast associated with the formation of small cysts. It is accompanied by evidence of hypo-ovarianism with pituitary overactivity. It may be treated by the cyclical use of œstradiol dipropionate and progesterone, or by œstrogens alone given in the mid-interval. Regression of symptoms after three or four months is not unusual and a further course of treatment is required. (2) *Cystic hyperplasia* (mastodynia) is the more common type, being associated with cystic ovarian disease and oversecretion of œstrogens. This is characterized by well circumscribed cysts in the centre of the breast due to continuous proliferation. Complete symptomatic relief can be obtained, usually without recurrence by the use of testosterone propionate, 25 mg., once or twice daily for two or three days. This depresses œstrogenic activity completely. It is well to note that the period immediately following this procedure may be scanty, delayed or absent. We have also used testosterone propionate in gynæcomastia associated with adolescence, with excellent results. In these a weekly injection of 25 mg. for two or three months is very effective in allaying the pain and reducing the size of the breasts.

PREGNANCY

Threatened abortion, habitual abortion, premature labour.—The endocrine basis for the use of progesterone in these cases rests on the fact that the placenta functions normally as an endocrine gland producing progesterone. The well established decrease in the excretion of pregnandiol which accompanies these complications of pregnancy provides the rationale for the use of progesterone. The dosage is outlined adequately in the synoptic table, and it is only necessary to recall that the amounts given must be very large if a good response is to be expected. The normal pregnant woman excretes up to 20 mg. a day at the third month, and replacement must be at least the equal of that quantity daily during the time when symptoms are present.

COMMENTS

More than thirty years have passed since ovarian extracts were first prepared for clinical use. In recent years the earlier crude extracts have given place to pure crystalline preparations and then to synthetic ones. In many cases, the synthetic materials have been shown to provide even greater biological activity than those produced naturally. That these should be added to our therapeutic armamentarium is obviously a step in the right direction. This paper is an attempt to present the salient information about the sex hormones, their function, and their use in the more common disorders of the female genital tract (Table V). The information has been gathered from many sources, but the form of treatment outlined is based on our own clinical experience and in most cases is in accord with that of many other investigators.

Acknowledgment is made to the Associate Committee on Medical Research of the National Research Council for assistance through a grant to Professor G. Hunter.

The authors are indebted to Mr. E. R. Angehrn, of the Ciba Company, Montreal, for his generosity over a period of years.

THE PATHOGENESIS OF CHRONIC ATROPHIC PYELONEPHRITIS AND ITS POSSIBLE RELATION TO THE PRODUCTION OF HYPERTENSION

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IT is now a well established fact that hypertension may be produced by causing an ischæmia of the kidney, either by the method developed by Goldblatt[1, 2, 3] of clamping the renal artery, or by Page's[4] method of inducing a perinephritis by wrapping the kidneys in cellophane. Subsequently it was shown by Page,[5] Munoz *et al.*,[6] Corcoran and Page[7] and others that the hypertension was apparently due to the formation of a substance called renin in the ischæmic kidney which combined with a pseudoglobulin in the blood serum, to form a vasoconstrictor substance angiotonin. An inhibitor substance, termed hypertensinase by Munoz,[6] was also demonstrated in the normal kidney which counteracted the action of the angiotonin. This inhibitor substance has also been isolated by Page[8] and his colleagues who have reported beneficial results in the treatment of both human and animal hypertensives by its use. The basis of experimental hypertension thus appears to depend on what might be termed the "inhibitor-angiotonin" balance.

Many papers have recently appeared attempting to correlate cases of clinical hypertension with an ischæmia of the kidneys. Those appearing to have the soundest basis deal with chronic atrophic pyelonephritis; for instance Barker and Walters,[9] in reviewing 57 such cases diagnosed clinically, found 45.5 per cent with an elevated blood pressure, while in 24 cases with a pathological diagnosis 62.5 per cent had a raised pressure and 45.8 per cent definite hypertension. Other papers, such as those by Butler,[10] Barney and Suby,[11] Patch, Rhea and Codnere[12] and others, report relief of hypertension in cases of unilateral chronic pyelonephritis treated by nephrectomy.

Weiss and Parker[13] in an excellent review of the pathological changes occurring in such cases, suggest that a renal arterio- and arteriolosclerosis resulting from inflammatory damage and leading to an ischæmia, is the probable cause of the hypertension. This theory however cannot be accepted as the entire etiological factor since Crabtree and Chaset,[14] reporting 150 consecutive nephrectomies, found that vascular changes were present in a large percentage of cases with no hypertension, which is a common surgical pathological finding.

Braasch *et al.*,[15] in analyzing 1,684 patients subjected to renal operation for various conditions, found the incidence of hypertension no higher than in patients taken at random. They state, however, that atrophic pyelonephritis with associated hypertension forms the group most amenable to surgical treatment for the relief of the raised pressure, and they predict that surgery may relieve it in 70 per cent of these cases. It would thus appear that hypertension is not associated with the vast majority of surgical renal conditions, but that in a small group of chronic pyelonephritic cases, hypertension is present and seems to be related to the renal condition, and is not merely a coincidental finding. The following cases are reported in an effort to explain this associated hypertension.

Case 1

Mrs. H.C., aged 34 years, was admitted to hospital in 1935 with an epithelioma of the cervix which was treated with radium. Her blood pressure was recorded as 130/95, and one urine examination revealed nothing abnormal. She was discharged after one month, still with a foul P.V. discharge.

In 1941 (six years later) she was readmitted complaining of sciatica which had commenced two months previously. The pain radiated down the back of her right leg to the sole of her foot. Physical examination proved negative except for tenderness over the sciatic nerve. Because of the previous history it was suspected that pressure from metastases in the vertebral column might be the cause of the pain. X-ray of all bones, however, proved negative, and pelvic examination showed no evidence of the previous carcinoma. The blood pressure was now 160/105. Repeated urine examinations revealed a few pus and red cells and occasionally a hyaline and granular cast. Albumin was negative. Lumbar puncture and examination of the urine for lead also proved negative. Blood chemistry on admission was within normal limits, but just before death it had risen to a high normal; non-protein nitrogen 42.54, urea nitrogen 19.83, uric acid 5.48 and creatinine 1.71. She was in bed continuously, and 20 days after admission her temperature rose to 102°, at which time she complained of headache and respiratory distress, which gradually became worse until she lapsed into coma and expired.

Post-mortem examination revealed an acute suppurative bronchiolitis with marked toxic change in the liver and spleen. The left ventricle of the heart showed a little concentric hypertrophy.

Left kidney.—This organ was reduced to less than half of its normal size, the capsule was difficult to strip and the surface was deeply scarred, while the intervening tissue was somewhat granular. The pelvis was slightly dilated, but there was no evidence of

acute inflammatory change. Histological examination revealed large patches of completely sclerosed glomeruli and wide destruction of tubules with marked infiltration of lymphocytes. The glomerular lesion consisted of a periglomerular fibrosis which extended inwards causing complete obliteration of the vascular tuft (Fig. 1). There was an early degree of periglomerular fibrosis in some small areas of fairly normal tissue which alternated with the larger areas described. This early perifibrosis was similar to that usually seen in hydronephrosis and in those cases of pyelonephritis with no associated hypertension. The interlobular arteries showed a little endarteritis, with slight narrowing of their lumina and there was a minimal degree of arteriolosclerosis dissimilar to that seen in essential hypertension.

Right kidney.—This was normal in size and appearance. Histologically, however, there were a few fibrosed glomeruli occurring in small scattered patches, and a minor degree of arterio- and arteriolo-sclerosis. There was no generalized arteriosclerosis in the other organs.

end did he complain of abdominal pain. Urine examination showed a one plus albumin, but no pus cells or red cells were seen on microscopical examination. The blood urea nitrogen was 12.32.

Post-mortem examination.—There was an acute suppurative peritonitis due to a perforated acute duodenal ulcer. Several shallow chronic ones were also present, but the patient had never complained of indigestion or abdominal pain. The left ventricle of the heart showed a moderate concentric hypertrophy.

Right kidney.—There was a hypernephroma involving the upper third of the organ and there was also a marked hydronephrosis, only a small portion of normal-looking tissue remaining at the lower pole. The kidney between this and the tumour was fibrotic and scarred.

The histological findings were almost identical with the previous case. Fig. 2 shows the marked tubular destruction with lymphocytic infiltration and varying degrees of glomerular fibrosis which can definitely be seen to be progressing from without inwards. The periglomerular fibrosis was more marked than in Case 1 and less completely sclerosed glomeruli were present.

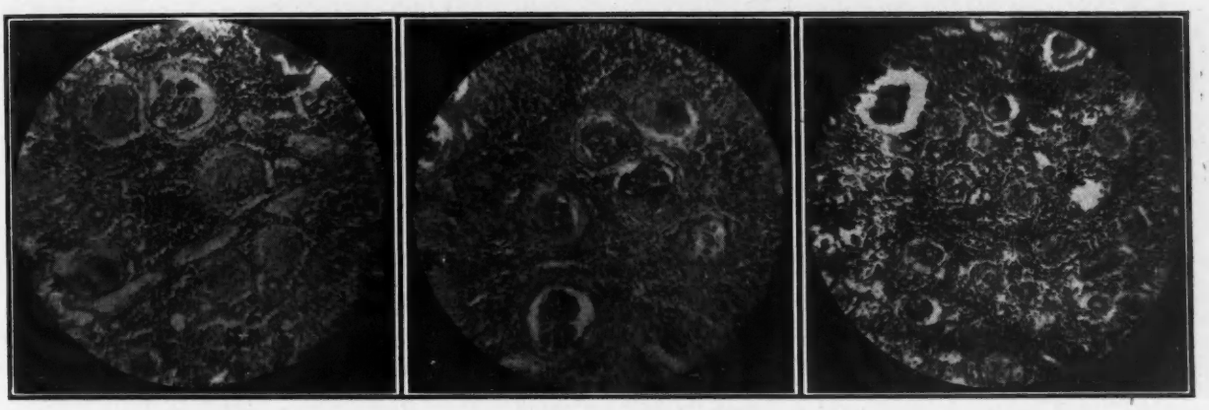

Fig. 1 **Fig. 2** **Fig. 3**

Fig. 1.—Photomicrograph of left renal cortex from Case 1, showing marked tubular destruction with lymphocytic infiltration and varying degrees of glomerular fibrosis progressing from without inwards. H and E stain. Medium magnification. **Fig. 2.**—Photomicrograph of right renal cortex from Case 2. The pathology is similar to Case 1. Note the definite periglomerular fibrosis extending inwards and obliterating the vascular tuft. H and E stain. Medium magnification. **Fig. 3.**—Photomicrograph of right renal cortex from Case 3. Note the numerous fibrosed glomeruli in the field with marked lymphocytic infiltration and tubular destruction. H and E stain. Low magnification.

In brief the findings were a unilateral chronic pyelonephritis with associated hypertension and a minimal degree of glomerular fibrosis and arteriosclerosis in the contralateral kidney. It is of interest to note that the uterus was only the size of a walnut and microscopic examination failed to reveal any tumour cells. The sciatica was undoubtedly due to a mass of adhesions in the pelvis. There is a possibility that the renal infection was related to the old cervical lesion; however there was no evidence to support this supposition.

CASE 2

K.P., a male, aged 70 years, was admitted to hospital with acute retention. One week previously his blood pressure was 190/100. The retention was relieved by fixing a catheter in the bladder. Shortly after, he appeared to be in shock and passed a large tarry stool, followed by bright blood. His condition deteriorated rapidly so that a thorough examination was not possible. A transfusion was given but on the following day he once more became shocked and expired a few hours later. At no time until the very

The interlobular arteries, however, showed more endarteritis, with narrowing of their lumina. The degree of arteriolosclerosis was also slightly more marked, but they did not show the usual hyalinization seen in essential hypertension. The pelvis showed a typical chronic inflammatory change.

Left kidney.—There was only a minor degree of hydronephrosis and the surface was smooth, the cortex of normal width and the markings distinct. Histological examination revealed some glomeruli with periglomerular fibrosis and very slight arteriosclerosis. The arterioles were not affected. The prostate was enlarged due to a simple adenomatous hyperplasia and the urethra was obstructed, the bladder wall being hypertrophied and trabeculated. No generalized arteriolosclerosis was present in the other organs examined.

Summary.—Unilateral chronic pyelonephritis with hydronephrosis and hypernephroma of right kidney associated with hypertension and a slight hydronephrosis with early periglomerular fibrosis in the contralateral kidney.

CASE 3

This is of particular interest since the patient was a child aged 5 years. He was in hospital in 1937 with a scalp injury which became infected, resulting in a sinus formation. During his three months' stay in hospital several urine examinations were done and found negative, but just before his discharge 20 pus

cells per high power field were found. One can therefore assume that either a bladder or kidney infection was present at that time, perhaps associated with the infected scalp wound. He was never in good health after that.

In 1941 he was readmitted to hospital because of headache and listlessness. On the day previous to admission, he had fallen and hit his head. Just after entering the hospital twitching of his body occurred and this continued in spite of chloral hydrate administered per rectum, until his death 14 hours later. Unfortunately no urine analysis or blood pressure readings were recorded.

Post-mortem.—There was a marked concentric hypertrophy of the left ventricle, the wall at its thickest point measuring 1 inch in width. The valves and pericardium were normal so that one may assume an existent hypertension to account for such marked left ventricular hypertrophy. There was a small subdural hæmorrhage of the brain underlying a hæmatoma of the scalp, otherwise the pathological changes were confined to the genito-urinary tract.

Kidneys.—Both organs were extremely shrunken and scarred. The mucosa of the pelves was thickened and they were dilated. The cortices were irregularly thinned, due to large wedge-shaped fibrotic areas, and this, associated with the dilated pelvis, left only a thin rind of kidney parenchyma. The ureter on the right side was slightly dilated and tortuous, while the bladder showed a fibrotic thickening due to a chronic cystitis. Histological examination revealed similar lesions in each organ. Only a few small areas of fairly normal looking tissue were left, the remainder showing the same changes as in the two previous cases; marked tubular destruction with lymphocytic infiltration and glomerular fibrosis (Fig. 3). There were more completely sclerosed glomeruli in this case, and the interlobular arteries showed marked sclerosis, both endarteritis and medial hypertrophy with reduplication of the elastica interna being present. The arterioles were also more sclerotic than in the other cases and some hyalinization was noted. The arterioles in the liver, spleen and pancreas were also sclerotic.

Summary.—Bilateral chronic atrophic pyelonephritis with associated hypertension, uræmia and generalized arteriolosclerosis.

DISCUSSION

The essential lesion in these three cases is the destruction of large numbers of glomeruli by a fibrotic process of inflammatory nature, originating from an ascending infection in the tubules leading to a periglomerular fibrosis, complete obliteration of the vascular tufts, and a varying degree of arterio- and arteriolo-sclerosis. Such a reaction must of necessity lead to an ischæmia of the kidney, so that one may safely assume the release of renin and the subsequent formation of angiotonin with production of hypertension in a manner similar to that obtained in experimental hypertension. It should be emphasized that the renal and general arterial changes in the cases presented are not in the least similar to those seen in essential hypertension, except in Case 3, which was a five-year old boy in which the presence of the essential type of hypertension can of course be ruled out.

In Case 2 there was the additional factor of a hypernephroma involving and destroying the upper portion of the affected kidney. It is conceivable that the tumour may further have aggravated the ischæmia by pressure, comparable to the method used by Page[4] in obtaining experimental hypertension by means of cellophane perinephritis. A case of hypertension in a seven year old girl with a Wilm's tumour, relieved by nephrectomy, has in fact been reported by Koon and Ruch,[16] and in their paper they suggest that the raised pressure was due to interference with the renal blood supply by pressure of the tumour.

The association of hypertension with cases of unilateral chronic pyelonephritis is, however, difficult to understand, for one would expect the inhibitor substance present in the normal kidney to prevent the rise in pressure. It is possible that the so-called "normal kidney" is not histologically normal, but that a minimal degree of fibrosis may be present, sufficient to upset the "angiotonin-inhibitor" balance. In the three cases presented here, the contralateral kidney showed pathological changes on histological examination, although in two of them the gross appearances were normal. That such may be the case, is suggested by Schroeder and Fish[17] who found in seven patients with hypertension, associated with chronic pyelonephritis and treated by nephrectomy, that although improvement was noted in each case "all remained actually or potentially hypertensive" thus suggesting damage to the remaining kidney.

One must also bear in mind the possibility of a vicious circle being initiated by the hypertension whereby the vascular bed of the kidneys, and other organs, may be further damaged due to the effect of the elevated pressure, and thus lead to more renal ischæmia. The presence of the generalized arteriolosclerosis in Case 3 was apparently due to such an occurrence. This type of reaction has been demonstrated conclusively in rats with experimentally induced hypertension by Wilson and Byrom.[18] Because of this possibility Schroeder and Fish,[17] Patch,[12] Palmer *et al.*,[19] have sounded a warning against removing a grossly diseased kidney in the hope of relieving hypertension, without first being sure that vascular damage is at least only minimal in the other kidney.

CONCLUSIONS

It is suggested that in order to have hypertension associated with chronic atrophic pyelonephritis, there must be sufficient vascular damage, either by progressive glomerular fibrosis or marked arteriosclerosis, to upset what has

been termed the "inhibitor-angiotonin" balance. One may find marked arteriosclerosis in one kidney without associated hypertension, because in such a case the inhibitor substance present in the normal kidney would counteract the action of the angiotonin released by the diseased ischæmic kidney; however, if the other kidney is sufficiently diseased to decrease the inhibitor substance, then the pressor substance can act unhindered and consequently hypertension would result.

It is possible that the same pathological process, with a different etiological basis, may explain the persistent hypertension in chronic glomerulonephritis, for in the latter there is also a progressive fibrosis of the glomeruli from the acute through the subacute to the chronic stage in which numerous sclerosed and obliterated glomeruli can always be demonstrated.

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CONTACT DERMATITIS OF THE FEET

BY J. F. BURGESS, M.D.

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THE increasing number of cases of dermatitis of the feet due to hypersensitization of the skin to various contacts, necessitates a careful etiological diagnosis in order to separate these cases from common coccal, ringworm or yeast infections, with which they may easily be confused.

Hypersensitivity to shoe leather has long been recognized. It is on the whole relatively rarely encountered. Similar reactions from dyed socks and dyed fabrics of overshoes are also not commonly seen. On the other hand, eczematous reactions to other fabrics used in the manufacture of shoes, such as canvas and fabrikoid (*ersatz* leather), are being more commonly seen, particularly within the past two years. Undoubtedly, various chemicals used in the processing of these materials act as sensitizing agents.

The following cases are recorded of an eczmatous dermatitis, involving that part of the feet more commonly associated with infectious processes, and closely simulating these conditions clinically.

CASE 1

SHOE LEATHER DERMATITIS

A.B., male, aged 52, presented a markedly exudative and scaly eczema, with a good deal of œdema of the sides and dorsum of the feet and toes. The condition had been present for one year with some periods of quiescence alternating with marked exacerbations characterized by great irritability. There was exudation but no actual maceration or demarcated scaling between the toes. He had always obtained his shoes from the same manufacturer. Patch tests to the leathers of his recently bought shoes (black, brown, and reddish brown) and later to a sample piece of sheepskin, were markedly positive. Tests made at the same time to canvas, fabrikoid and socks were negative. Microscopic examination of the scales for fungus was negative. The reactions to his leather persisted for many days, which was in keeping with the slow response to treatment, even after all contact with leather had been restricted. He was able to find a leather to which he was not sensitive. He was treated with compresses, and other soothing applications, along with x-ray therapy and made a slow recovery.

CASE 2

CANVAS DERMATITIS

J.M., male, aged 55, in July, 1940, developed a mildly irritating eruption, on the dorsum of his feet, apparently coincident with the wearing of a pair of canvas shoes. He did not wear them again. In September the irritation and eczematous reaction flared up again, being at times intense and at other

times less marked. When seen in October, a marked eruption, erythematous and somewhat exudative and scaly in character, was present on the dorsum of the ankles and involving the toes and slightly along the lateral aspect of the mid part of the ankles. The soles and opposing parts of the toes were clear. He had acquired two new pairs of shoes in August from the same firm with which he had dealt for years. Examination of the shoes revealed that the eruption exactly coincided with the distribution of the canvas lining of his shoes. Patch tests were done with canvas, leather and socks and the reactions to these were negative. A further patch test to canvas applied over the eczematized area was strongly positive. Recovery followed fairly promptly when all canvas had been removed in his shoes. Soothing applications only were used.

CASE 3

A.McK., female, aged 18, presented a marked exudative œdematous dermatitis of the feet which had been recurring over the past three months, following the buying of a new pair of shoes one month prior to the onset of the eruption. The distribution of the eruption exactly coincided with the distribution of the canvas lining of her shoes and is depicted in Figs. 1, 2 and 3. Patch tests were strongly positive to her canvas lining and persisted as a small eczematized area for two weeks. Recovery followed the removal of the canvas lining.

These cases are typical of other cases of this kind seen within the past two years. The cause would seem to be due to some recent change in the processing of canvas lining.

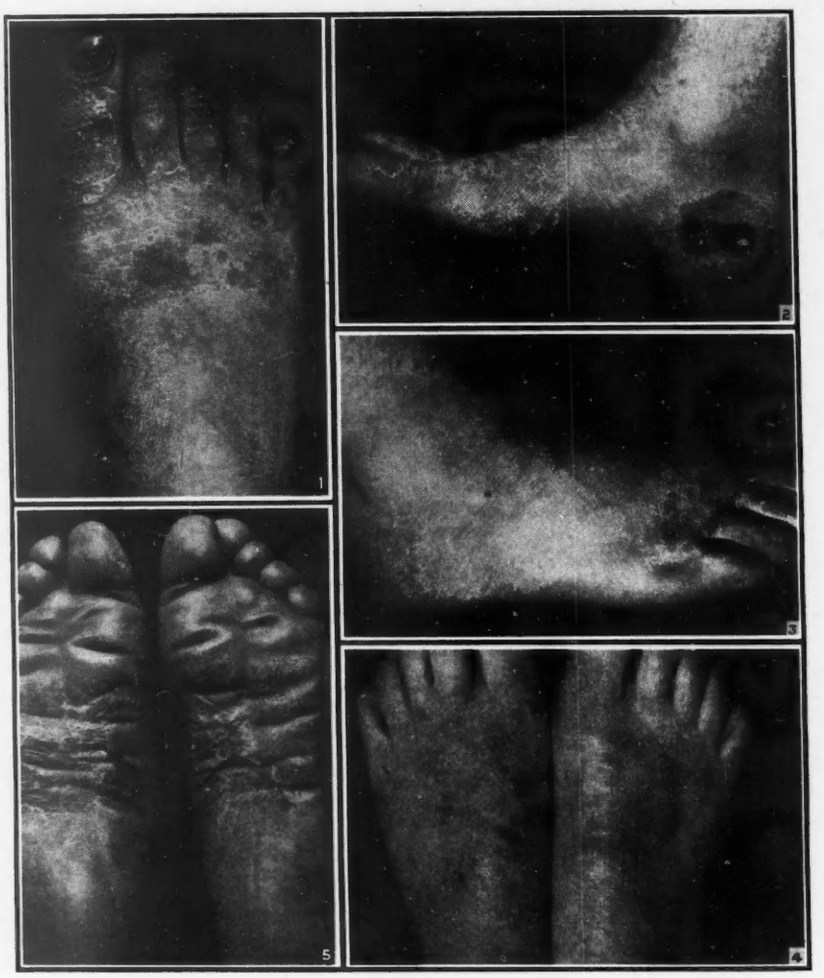

Fig. 1, Case 3.—Canvas dermatitis. Marked eczematous dermatitis of dorsum of feet. **Fig. 2**, Case 3.—Canvas dermatitis. Distribution of the eczematous dermatitis along the sides of the feet. **Fig. 3**, Case 3.—Canvas dermatitis. Distribution of eczematous dermatitis along the sides of the feet. **Fig. 4**, Case 4.—Fabrikoid dermatitis. Eczematous dermatitis on dorsum of ankle. **Fig. 5**, Case 4.—Fabrikoid dermatitis. Vesico-pustular and scaly eczematous dermatitis on sole of feet.

CASE 4

FABRIKOID DERMATITIS

B., female, aged 22, in February, 1941, presented a marked vesico-pustular and inflammatory dermatitis involving the middle portion of the soles of the feet, the dorsum of the ankle and the toes slightly (Figs. 4 and 5). The eruption closely simulated a ringworm infection but microscopic examination was negative for fungus. The eruption had been present for two months. Owing to the severity of the eruption, she was admitted to the hospital. Patch tests with leather, canvas and fabrikoid of her shoes showed a marked positive reaction to fabrikoid only. Treatment consisted of soothing applications and x-ray therapy. On discharge from the hospital her shoes were changed and other lining was substituted for fabrikoid. No further involvement of the feet has occurred.

CASE 5

COTTON SOLE DERMATITIS

R.T.B., female, aged 57, presented an acute erythematous and somewhat œdematous dermatitis involving the soles of the feet and toes, and extending about 1" above the line of the soles about the circumference of each foot. She had had this condition for one month, and at times mild vesiculation was seen. Itching was marked. She also presented small eczematous scaly patches on the dorsum of the hands and slightly about the neck, which was of more recent origin. She had bought two new pairs of stockings one month before the onset of the eruption and attention was directed to these as a possible cause. She was therefore patch-tested with the lining of bedroom shoes, shoes, leather, canvas and the upper ravon and the cotton sole part of her new stockings. The reaction to the cotton sole was strongly positive, whereas all other patch tests were completely negative. On discarding these stockings, and under bland applications and x-ray therapy the eruption made a slow recovery.

This case probably is etiologically connected with those cases of eczematous dermatitis caused by cotton fabrics in various types of garments seen very commonly in the past three years and shown to be due to resin used in the processing.

SUMMARY

Cases, representing examples of shoe leather, fabrikoid, canvas and cotton-sole dermatitis of

the feet are recorded. The clinical picture in many cases simulates epidermophytosis of the feet from which it is to be differentiated. The diagnosis is made on the clinical picture, the history of contact with relatively new shoes or new stockings, the use of patch tests to contacts and the absence of fungus on microscopic examination.

RÉSUMÉ

De plus en plus, les dermatites des pieds chez les sujets dont la peau est hypersensible aux divers contacts nécessite un diagnostic étiologique précis pour ne pas ccnfondre ces états avec les coccies ou les affections causées par les levures. Les cuirs inférieurs, les ersatz et les teintures sont à la base de ces dermatites. Cinq de ces cas de dermatite eczémateuse sont rapportés. Cliniquement on peut croire à l'épidermophytose. Le diagnostic se fait par l'anamnèse, par la notion de contact avec des souliers relativement neufs, par l'utilisation des "patch-tests" et par l'absence de levures à l'examen microscopique.

JEAN SAUCIER

SUPPURATIVE PAROTITIS*

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SUPPURATIVE infections of the parotid gland have received scant attention in Canadian medical literature for over a decade. Recent improvements in treatment are so eminently satisfactory that it would seem an opportune time to call attention to this condition.

Appearing with almost dramatic suddenness, parotitis is not only an exceedingly painful and annoying but also a serious complication of surgery. Maurer,[7] emphasizing its gravity, reported 14 deaths among 33 cases, a mortality of 42 per cent. While it is true that this high mortality is in large part due to the primary disease process, the added suffering and toxicity of the parotid infection are apt to prove more than the already taxed patient can withstand.

The infection usually reaches the gland from the mouth via Stensen's duct. Experimentally, parotitis can be produced by injection of organisms into the nutrient artery, and the possibility of embolic infection of the patient also exists. The organism in most cases is said to be the *Staph. aureus*. Next in frequency is found the pneumococcus, and, lastly, the streptococcus. Henderson,[5] discussing the etiology of the disease, states that any lowering of general body resistance favours an increase in virulence of the normal buccal bacterial flora. The diminution of salivary secretion and flow which occurs in the presence of fever, dehydration, vomiting or a restriction of oral fluids favours an ascending infection of the gland. Salivation ceases for some hours following general anæsthesia and there is also the possibility that mechanical pressure on the gland by the anæsthetist may occur and tend to lower its resistance to infection. Pavlov also has demonstrated a reflex cessation of salivary flow accompanying laparotomy and visceral manipulation.

Blair and Padgett,[1] discussing the primary conditions upon which this complication most frequently supervenes, list the following: (1) as part of a post-operative complex; (2) following an infected wound in any part of the body; (3) in the course of any acute infectious disease, particularly typhoid and pneumonia; (4) in any severe asthenic state; (5) as a terminal condition. The present series would appear to substantiate these conclusions.

Prophylaxis must include (1) adequate pre- and post-operative oral hygiene and dental care, mouth washes, etc., being particularly stressed; (2) maintenance of general well-being, correction of vitamin deficiencies and so forth.

Probably the greatest contribution to the treatment of acute infections of the parotid gland was made by Rankin and Palmer[8] in 1930. These authors showed that the immediate use of radium over the infected gland materially reduced the incidence of suppuration and thereby the morbidity and mortality. A large dose was not necessarily more effectual than a medium-sized one. The main necessity was early application. They gave a maximum of 4 treatments, each of 8 hours' duration and at 8 hour intervals: 200 mg. of radium, filtered by approximately 1 mm. of platinum, were used at 2.5 cm. skin distance. The maximum dose thus given was 6,605 mg.-hours. The minimum was 2 applications each of 50 mg. for 8 hours at 8 hour intervals, totalling 800 mg.-hours. There was no change in the first 24 to 48 hours follow-

* From the Neoplastic Service, Metropolitan General Hospital, Windsor.

ing treatment and then a rapid subsidence took place. Surgical intervention was rarely necessary, and the mortality was greatly reduced, being only 5 per cent as compared with a reported 33 per cent mortality among a non-irradiated group compiled from various authors; (26.6 per cent in Henderson's series and 42.8 per cent in the cases collected by Blair and Padgett). Several authors confirmed these results. Bowing and Fricke,[2] of the Mayo Clinic, in 1936 reported the use of radium 184 times for post-operative parotitis with very gratifying results. There were no detrimental effects and no contraindications. The latter author, reporting again in 1939, stated that radium treatment of acute post-operative parotitis had been even more successful during the preceding two years owing to more prompt recognition of the disease and the earlier institution of treatment. If treated at the inception suppuration and abscess formation were aborted and resolution occurred.

It is interesting to note that the seventh edition of Thomson and Miles' *Surgery*, published in 1926, rather hastily mentions the use of radium and x-ray therapy as being of some possible benefit in non-suppurative recurrent enlargements of the gland. The author has encountered no reliable mention of x-ray treatment of acute parotitis, however, until Hodges[6] wrote in 1936 that most acute, sub-acute and chronic cases almost uniformly responded well with from three to five doses of 125 r of x-radiation, delivered at 125 k.v. and filtered by 4 to 6 mm. of aluminum. Hodges called attention to the fact that he had in 1924 reported the successful treatment by this means of 5 sub-acute and chronic cases. Robinson and Spencer also reported similar results in 12 cases from the Massachusetts' General Hospital. Desjardins,[4] of the Mayo Clinic, in 1937 agreed that roentgen therapy was just as effective as radium treatment, but felt that in many cases the latter was preferable because it could be given without disturbing the patient. Crile[3] believes that roentgen therapy is the treatment of choice if given immediately and states that any portable machine whose output is known may be used. He has used sulfathiazole as a supportive measure. Kaplan says that either radium or x-ray is almost a specific, if used early.

The presently reported series was begun in 1937 at a time when the above mentioned reports were commencing to appear. We have at our disposal more than the 200 mg. of radium recommended by the Mayo Clinic workers, but decided to use 200 k.v. roentgen therapy, believing it to be essentially the same therapeutic procedure and much less time-consuming and troublesome to both staff and patient. This treatment has now been carried out on a series of 20 patients. Actually there were 19 cases of parotitis, 6 of which had bilateral involvement. The 20th case was one of bilateral submaxillary adenitis. This condition would appear to be similar in nature but for some reason is much less frequently encountered. The incidence was the same for both sexes—10 cases occurring in males and 10 in females. The age of the patients varied from 13 to 83 with a mean of 41 years. It has been stated[5] that parotitis has a seasonal trend parallel to the incidence of upper respiratory infections and that most cases occur between November and April. This trend is not borne out by the present series, in which no case occurred during November or December, although 13 were in the first half of the year and only 7 in the second half. Sixteen cases followed upon an operation. Five of these operations involved the pelvic organs or large bowel. This would appear to substantiate Rankin's statement that parotitis occurs seventeen times as frequently following operations on the colon as in the general surgical group. A very large percentage were definitely poor risk patients, and oral infection was a common accompaniment.

Of the 16 surgical cases, 6 had ether anæsthesia, 1 had chloroform, 5 spinal, 3 local, and 1 had a spinal anæsthetic followed by ether four days later and one day prior to the onset of the parotitis. Inasmuch as the patients developing parotitis after spinal anæsthesia had in large part been subjected also to colonic or pelvic operations, the procedures most commonly followed by parotitis, we are inclined to believe that the incidence is less with spinal than with ether anæsthesia. This is probably because of the less frequently associated vomiting. All cases in whom local anæsthesia had been used had definite severe oral sepsis. Eight of the entire series of 20 were either vomiting shortly before the onset of the parotitis or had an indwelling tube for feeding or Wagensteen suction purposes. We have been impressed with the difficulty of keeping these tubes in a clean condition and inasmuch as 6 of our series had such a tube in place, we are inclined to feel that while it is a valuable adjunct to surgery it neverthe-

less requires careful attention and is a definite cause of oral infection and resultant parotitis. Five cases were getting no oral fluids at the onset of the parotitis. The majority were receiving adequate parenteral fluids. The parotitis developed from 1 to 21 days post-operatively. The mean was on the 8th day.

Treatment has been considered that of an emergency, requiring immediate x-ray therapy at any hour of the day or night. Important adjuncts are frequent mouth washes and irrigations, adequate fluids and stimulation of the salivary flow by the use of chewing gum. The patient has been moved in bed to the high voltage equipment and the involved area given 150 to 200 r measured in air, at 200 k.v. at 50 cm. skin target distance and filtered by 0.5 mm. of copper and 3 mm. of aluminum, or 1 mm. of copper and 4 mm. of aluminum and through an appropriate portal, usually 10 x 15 cm. in size. If bilateral involvement is present both sides are treated. If treated first in the morning most cases have been given a second similar exposure late in the afternoon. 150 to 200 r is given on each succeeding day until adequate improvement results. The average case obtains marked relief from pain almost immediately and a lowering of temperature ensues. The gland is apt to show no objective change or perhaps may even be somewhat larger on the second day but then rapidly resolves. We have felt no necessity of using chemotherapy. The following typical case-histories are illustrative.

CASE 1

L.B., female, aged 23 years. She had had an appendectomy on February 21, 1940, under spinal anæsthesia and on the following day aborted a 3 to 4 weeks' fetus. A foul discharge persisted and pelvic peritonitis developed accompanied by vomiting.

On March 14th she was referred with a bilateral parotitis of 2½ hours' duration. Each gland was about 7 cm. in length. A dosage of 150 r was immediately given to both the right and the left sides of the neck and the dose was repeated on the 15th. The swelling of both parotids had entirely disappeared by March 17th. The total dosage was 300 r to each side of the neck. She had a prolonged illness from pelvic peritonitis, but ultimately recovered.

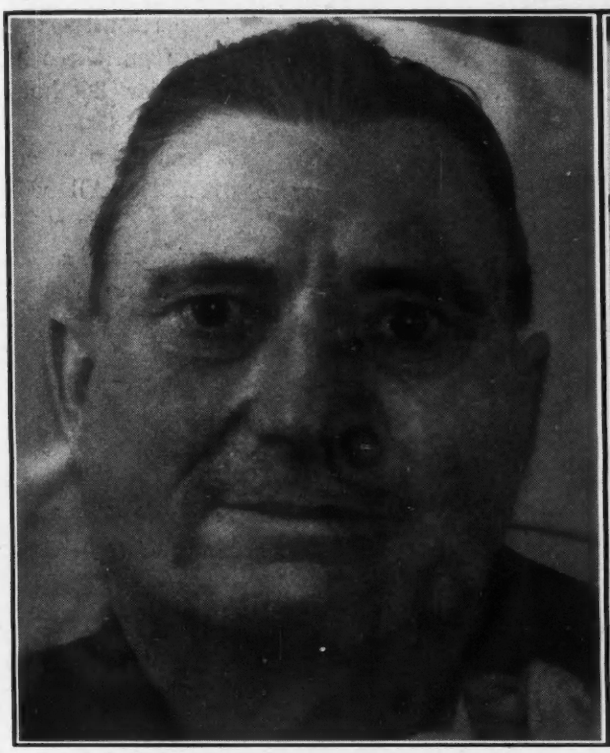

Fig. 1

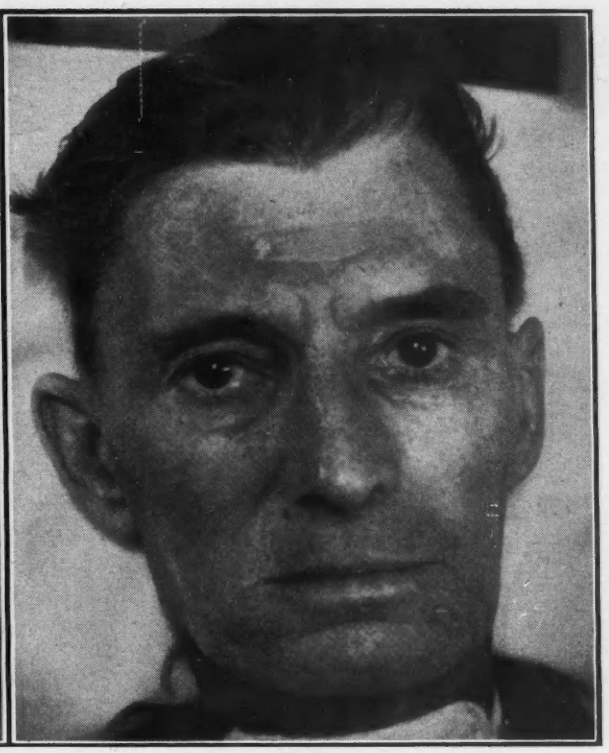

Fig. 2

Fig. 1, Case 3.—Bilateral acute post-operative parotitis. Marked swelling of both parotids.
Fig. 2, Case 3.—After irradiation. Complete subsidence of swelling.

CASE 2

C.E., a boy, 16 years of age, was operated upon under spinal anæsthesia for an acute suppurative appendicitis on March 13, 1940. He had an uneventful post-operative course and was receiving adequate oral and parenteral fluids. His mouth was free from obvious sepsis and there was no vomiting. At 2 p.m. on March 16th he began to complain of pain in the right side of his face and swelling was noticed. He was referred for treatment 6 hours later. At this time his temperature, previously 99.2°, had risen to 100° and the parotid measured 7 x 5 cm. in size and was exquisitely painful. He was given 150 r measured in air at 200 k.v. 50 cm. S.T.D. filtered by ½ mm. Cu. and 3 mm. Al. through a 10 x 15 cm. portal. A similar dose of 150 r was given on the 17th. There was very little, if any, change in size of the gland,

but the patient was quite comfortable and free from pain. On March 18th the gland measured 3 x 2 cm. and on the 19th was normal. Total dose 300 r. Mouth washes and chewing gum were used as supportive measures.

CASE 3

H.P., male, aged 62. This patient, suffering from an extrinsic carcinoma of the larynx, received intensive heavily filtered 200 k.v. x-ray therapy totalling 8,225 r to his neck in January and February of 1941. For some months afterwards his condition was quite satisfactory, but during the latter part of the summer he began to experience considerable difficulty in breathing and on August 19th was having marked laryngeal spasms. A tracheotomy was performed under local anæsthesia. The immediate post-operative course was uneventful, but as the patient found swallowing to be painful and difficult, a Levine nasal tube was inserted on the 22nd in order that he might be adequately fed. About 8.30 p.m. on August 29th the nurse observed swelling of both parotids, but this was not reported until the following morning. At this time his temperature previously 98.0° was 100.6°. A well developed bilateral parotitis was present. The gland on the right side measured 7 x 5 x 2 cm.—that on the left 7 x 6 x 2.5 cm. Both glands were very painful. He was immediately given 200 r to each side of the neck 12½ hours after onset of the parotitis and with the following factors—200 k.v. 50 cm. S.T.D. 10 x 15 cm. field and filtered by 1 mm. of Cu. and 4 mm. of aluminum. The glands were noticeably larger at 3 p.m. (Fig. 1) and the treatment was repeated.

On August 31st he was considerably more comfortable, but both glands were still swollen and an additional 200 r was given to each. Similar treatments were given on September 1st, at which time both glands were smaller and the patient was quite comfortable. On September 2nd the right parotid was normal. The left was still slightly swollen and was given an additional 200 r. The total dose—right 800 r, left 1,000 r. Complete regression ensued (Fig. 2). The patient died 5 weeks later of cancer but with no further parotid trouble.

Our series of 20 cases showed the following.

1. That 8 cases were treated within 6 hours of the onset of symptoms. A complete cure resulted without drainage in this entire group.

2. That 5 cases were treated within 7 to 16 hours after onset. One, a non-operative case, died in 36 hours of coronary disease with no noticeable improvement in the parotid. One subsided satisfactorily with a slight purulent discharge from the ear. Three were completely cured of the parotitis without incision or spontaneous drainage, but one of these died 5 weeks later of his primary disease, cancer. One of the cured cases, moribund immediately following admission and subsequently discharged from hospital seemingly well, developed a recurrence eight days later and this again subsided completely following further irradiation.

3. That 4 cases were treated within 17 to 24 hours. One died of intestinal obstruction due to cancer 4 days after the onset of bilateral parotitis and without obvious improvement. One died of cancer 2 weeks later with pus draining spontaneously from the ear, but with considerable diminution in the size of the gland. One subsided markedly but required incision 1 week later and the drainage of about 1 drachm of pus from each side of a bilateral glandular involvement. One resulted in complete cure without any drainage.

4. That 3 cases were treated after a lapse of time ranging from more than 24 hours to 1 week. Two softened up rapidly and recovered after incision and slight drainage. Both had a much less painful, quicker and easier convalescence than similar, non-irradiated cases of the author's experience, although 1 subsequently died of cancer with a normal parotid. The third had a cure of one side of a bilateral parotitis of 12 hours' duration, but died of peritonitis with slight and spontaneous drainage from the other side, which had been involved for 34 hours before treatment.

The mortality of the series was 20 per cent. Four died with parotitis present. All were terminal cases dying of other causes. Two others survived the parotitis to die 4 and 5 weeks later respectively of cancer, but with no further parotid trouble. Delay in incision was usually rewarded. The swelling eventually subsided even in the slow cases, or became localized so that only a small incision was necessary.

CONCLUSIONS

Parotitis is a serious emergency and requires immediate treatment at any hour of the day or night.

When combined with suitable supportive measures 200 k.v. x-ray therapy can be considered practically a specific treatment, if instituted promptly.

Cases treated within 6 hours of the onset of the parotitis may be expected to resolve quickly.

If treated in from 7 to 16 hours many will yet resolve. The others respond well symptomatically, but may drain a small amount of pus spontaneously.

Cases seen 16 or more hours after onset should also be treated, as they may yet subside satisfactorily. If they do not subside completely, suppuration takes place more quickly and clears up sooner than in non-irradiated cases and there is considerable relief from pain.

Surgical intervention should be delayed, and if it becomes necessary consists of very simple incision.

Irradiation results in marked reduction of the morbidity and high mortality of this disease.

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DUPLICATION OF THE UTERUS AND VAGINA

BY GORDON E. PERRIGARD, B.A., M.D., C.M.

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THIS case, a primigravida, three months pregnant, presented herself for prenatal care. Upon examination it was discovered that she had two distinct vaginæ, two cervices and apparently two uteri, an anomalous condition similar to that seen in monotremes and the lower marsupials. This condition in the human subject is a result of the failure of the Müllerian ducts to fuse, the usual union taking place from below upwards. The patient was pregnant in the left uterus.

It was decided that it would be advisable to have the vaginal septum removed. Fig. 1 demonstrates the two vaginæ with the well formed septum between. The septum was quite vascular and thick. Fig. 2 is an attempt to demonstrate the two cervices, one at each end of the Allis forceps.

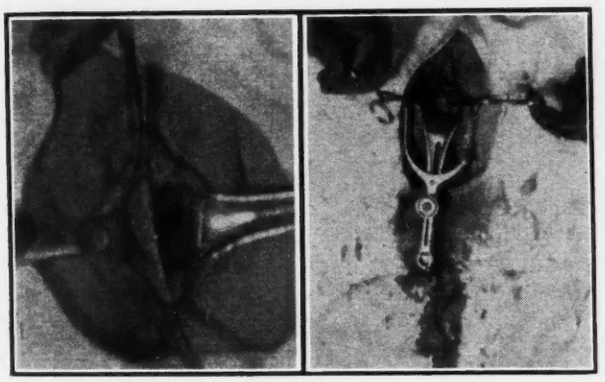


Fig. 1 Fig. 2

Fig. 1.—Two vagina with well formed septum between them. Retractor in each vagina, and volsella hold upper and lower limits of septum.

Fig. 2.—Vaginal septum has been removed and now two cervices are seen, one at each end of the Allis forceps.

The patient is maintaining her pregnancy without further mishap.

COMMENT

Besides this case, similar to the one reported by DeLee, of Uterus Duplex Bicornis, cum Vagina Septa, but where there was pregnancy in each horn, there are many other common anomalies of the female genitalia. See explanatory diagrams.

Uterine septa occur in Uterus Subseptus Unicorporeus with Septate Cervix, and in Uterus Subseptus Unicollis, or the bipartite uterus, which is a result of uterine primordia merging only at their lower ends and being partly separated by a median partition.

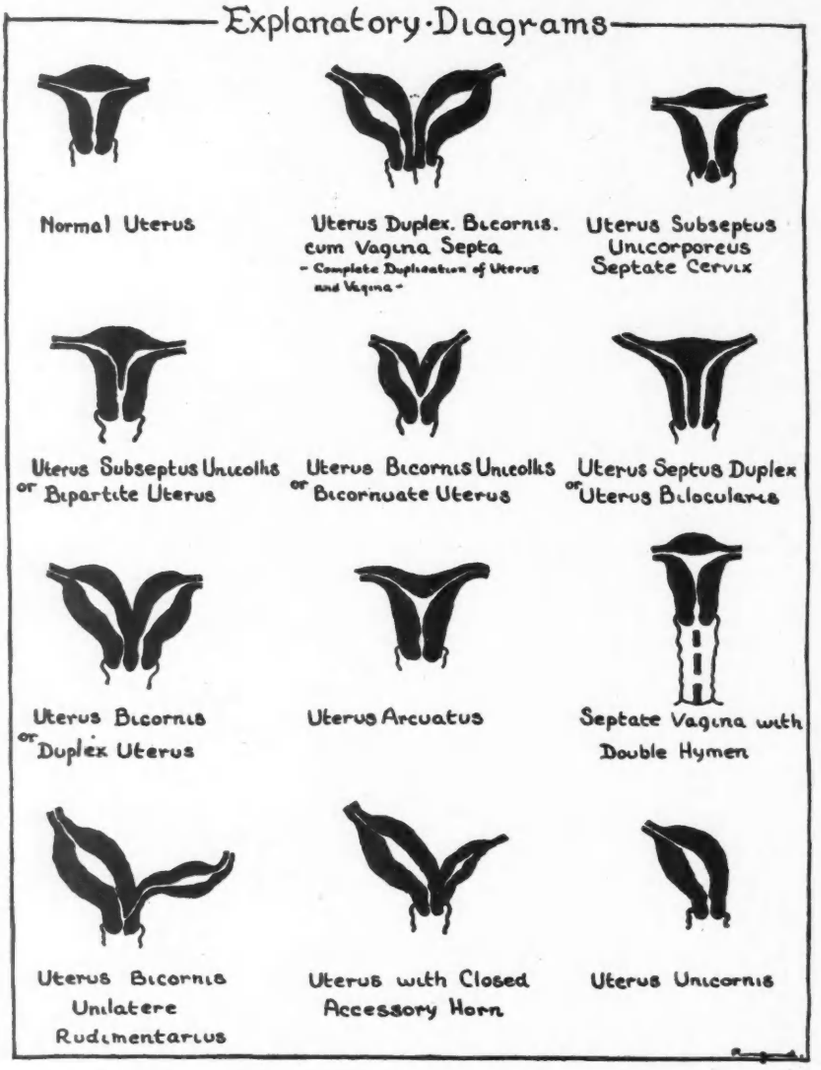
Another type of anomaly is the Uterus Bicornis Unicollis, or the bicornuate uterus, a condition which results from an imperfect absorption of the fundic segments which leaves paired pouches at the upper uterine ends. This condition may be observed in sheep. In the case of the Uterus Septus Duplex, or the Uterus Bilocularis, if the fundus also exhibits signs of division, it is called Uterus Bicornis, or duplex uterus, where there is a duplication only of the uterus and not of the vagina, evolved because of an arrest of uterine fusion. Most rodents exemplify this condition.

Uterus Arcuatus is one of the most common anomalies. Septate vagina with double hymen is also quite frequent; the septum may be situated at any point in the vagina or may exist throughout its entire length as in the case described here.

Other common anomalies include retention of the fetal or infantile conditions and malpositions. Also there may result congenital absence or lack of full development of one or both uterine tubes such as in Uterus Bicornis Unolatere Rudimentarius and uterus with closed accessory horn. Eighty per cent of rudimentary uterine horns have a canal which unfortunately does not communicate with the vagina (Ahlfeld, Munde, Santos). The possession of only one uterine horn, Uterus Unicornis, is normal in birds and does not generally interfere with

pregnancy in the human being. Like anomalies of the uterine tubes, there may also be absence or lack of full development of the uterus itself or of the vagina.

The vagina may remain partly or completely solid and the hymen frequently retains its primary imperforate condition. The incomplete fusion of the Müllerian ducts throughout the length of the canals, and rudimentary development of one duct may explain almost all of the anomalies. Varying degrees may run up from the Uterus Didelphys, one case of this demonstrating two complete distinct parturient canals with two vulvæ, a condition a little more marked than the one described here, to the common Uterus Arcuatus where the fundus uteri is indented in the middle. Diverticula of the uterus have been described and in one case the placenta was developed in an accessory uterine cavity connected with the main portion by a passage.


Explanatory Diagrams
Normal Uterus
Uterus Duplex. Bicornis. cum Vagina Septa
- Complete Duplication of Uterus and Vagina -
Uterus Subseptus Unicorporeus Septate Cervix
Uterus Subseptus Unicollis or Bipartite Uterus
Uterus Bicornis Unicollis or Bicornuate Uterus
Uterus Septus Duplex or Uterus Biloculares
Uterus Bicornis or Duplex Uterus
Uterus Arcuatus
Septate Vagina with Double Hymen
Uterus Bicornis Unilatere Rudimentarius
Uterus with Closed Accessory Horn
Uterus Unicornis

When there are two uteri, menstruation may come from both uteri simultaneously or from only one at a time. Müller reports cases of menstruation from the empty horn during a pregnancy. This is probably not a true menstruation. Labour is often quite normal, but complications have been observed, such as atony in the third stage with postpartum hæmorrhage; the nonpregnant part of the uterus may prolapse under the other and become incarcerated in the pelvis or it may show hypotonia and not contract, and, furthermore, if there exists a septum in the uterus this may not contract (Lorand) and the nonpregnant cervix may be pressed down to the vulva with the head of the baby. The uterus may rupture because of poor musculature, and vaginal septa may be obstacles. The septate uteri may cause breech and transverse positions, weak pains, postpartum atony, rigidity of the cervix, adherent placenta and if the septum is in the cervix there may occur obstruction to delivery, one case reported the septum being straddled (DeLee, Van de Velde, Ubbens, Findley).

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INFECTIOUS MONONUCLEOSIS WITH ACUTE THROMBOPENIC PURPURA*

BY WILLIAM MAGNER AND E. F. BROOKS

Toronto

WITH the exception of epistaxis, which is fairly common and may be severe, hæmorrhagic manifestations are rare in infectious mononucleosis. In 1921 Tidy and Morley[11] found that hæmaturia had been present in 6 per cent of 270 recorded cases of this disease, and in 1934 Tidy[10] collected reports of six cases showing purpura. It would appear, however, that the accuracy of the diagnosis in some of these cases is open to question (Minot,[7] Heck[5]). In 1936, Minot[7] described three cases of doubtful nature. In these there was acute thrombopenic purpura with high grade lymphocytosis (74 to 80 per cent) and many abnormal lymphocytes in the blood. The patients, aged 23, 21 and 10, showed mild fever with slight generalized swelling of the lymph nodes, and two showed enlargement of the spleen at the height of the disease. In two of these cases the Paul-Bunnell test was not done, in the other it was negative. All three patients recovered and there was no recurrence of purpura over periods of one to three and a half years.

Minot concludes that these cases are to be regarded as examples of purpura hæmorrhagica with atypical white cell response, rather than atypical infectious mononucleosis with pronounced thrombopenic purpura. In support of this contention, he quotes three other cases; also described in his paper, in which acute thrombopenic purpura with lymphocytosis occurred intermittently in women in association with menstrual periods. The case which we wish to report is in most respects similar to the first three of Minot's cases, but we believe that in our case a diagnosis of infectious mononucleosis is established, as the patient's serum showed the presence of the heterophile antibodies characteristic of that disease (Paul-Bunnell test).

CASE REPORT

E.O., a man aged 20, was admitted to St. Michael's Hospital on August 19, 1941. For one week he had suffered from severe nocturnal occipital headaches and tiredness, and for two days he had had slight pain in the region of the left lower ribs which was accentuated by deep breathing. On the morning of the day of his admission to hospital, he noticed that his urine was red and cloudy and that his legs were covered with hæmorrhagic spots. On the same morning he cut himself while shaving and bleeding continued for several hours. Later, on the same day, he began to ooze blood from the gum margins. Except for the common infectious diseases of childhood and an attack of rheumatic fever at the age of ten, he had been perfectly well until the onset of these symptoms.

Physical examination showed pallor, a temperature of 99.2° and a pulse rate of 80. The cardiac impulse was forcible and there was a rough mitral systolic murmur. The edge of the spleen could be felt just below the costal margin. There were numerous closely set petechial hæmorrhages on both legs and a small number on the anterior aspect of the chest and on the buccal mucosa. The inguinal lymph nodes were palpable and appeared to be slightly enlarged. The cervical and axillary nodes could not be felt. The bleeding time was 53 minutes and the clotting time 1½ minutes. There was albuminuria and gross hæmaturia. The clinical diagnosis at this stage of the investigation was acute thrombopenic purpura.

Examination of the blood showed a hæmoglobin percentage of 92 (Sahli), a red cell count of 4,950,000 and a leucocyte count of 18,800 with 13 per cent neutrophiles, 77.5 per cent lymphocytes, 8.5 per cent monocytes and 1 per cent eosinophiles. A platelet count was not done, but it was obvious from examination of blood films that these bodies were very greatly reduced in numbers. It was now clear that this was not an ordinary case of idiopathic thrombopenic purpura, as in that disease the percentage of neutrophile leucocytes in the blood is normal or, more usually, increased. It was decided that a diagnosis of acute leukæmia was untenable because of the absence of anæmia and the characters of the lymphocytes in stained blood films. About 20 per cent of these were normal small and medium-sized cells. Others were large with faintly basophilic cytoplasm and round or indented, heavily patterned nuclei devoid of nucleoli. In many of the cells the cytoplasm appeared foamy, spongy or vacuolated and contained few or many rather coarse carmine-red granules. In some cells the cytoplasm was strongly basophilic, particularly towards their periphery, but the nuclei showed the heavy chromatin network of the less basophilic cells and not the fine, spongy nuclear reticulum of the lymphoblast. Many of the nuclei of these abnormal lymphocytes were eccentrically situated, and a few showed small unstained areas having the appearance of fenestrations. While cells such as these may be found in the blood in subacute lymphocytic leukæmia, as well as in various infections associated with lymphocytosis, their presence in large numbers is very suggestive of infectious mononucleosis, particularly if anæmia is absent and the total white cell count is below ordinary leukæmic levels. With this diagnosis in mind a Paul-Bunnell test was done and was found to be positive with a serum dilution of 1 in 800.

The clinical course of the case was entirely satisfactory. The patient's subjective symptoms were at all times mild. No fresh petechiæ appeared after his admission to hospital. Hæmaturia and splenomegaly had disappeared by the sixth day. His temperature, which had not risen higher than 99.2°, was normal from the ninth day, and he was discharged in good condition on September 5th, sixteen days after the onset of hæmaturia and purpura. Subsequently he returned on four occasions for re-examination of his blood. The significant laboratory data in this case are summarized in Table I.

* From the Department of Pathology, St. Michael's Hospital, Toronto.

Read before the Section of Pathology, Academy of Medicine, Toronto, November 25, 1941.

TABLE I.

	20/8/41	25/8/41	3/9/41	12/9/41	19/9/41	26/9/41	10/10/41
Hæmoglobin (Sahli)	90	....	....	....	....	92	....
Red Cell Count	4.9	....	....	....	....	....	....
Platelet Count	greatly reduced	reduced	approx. normal	approx. normal	approx. normal	approx. normal	approx. normal
Leucocyte Count	18,800	13,000	11,200	10,150	8,700	6,000	9,400
Neutrophiles (percentage)	13.0	22.0	36.0	43.5	56.5	47.5	59.25
Lymphocytes (percentage)	77.5	74.0	60.0	44.5	33.5	45.0	35.0
Monocytes (percentage)	8.5	5.0	3.0	11.5	7.0	6.5	5.25
Eosinophiles (percentage)	1.0	....	1.0	0.5	3.0	1.0	0.5
Bleeding time	53 M.	....	....	....	....	....	....
Clotting time	1½ M.	....	....	....	....	....	....
Paul-Bunnell Test (Straus)	....	Positive 1/800	Positive 1/800	....	Positive 1/200	....	*A. Positive 1/10 B. Positive 1/10 C. Negative
Kahn and Laughlen Tests	Negative	....	....	....	....	....	....

*A = with untreated serum.
B = with serum treated with guinea-pig kidney tissue.
C = with serum treated with beef red blood corpuscles.

CLINICAL AND HÆMATOLOGICAL FEATURES OF INFECTIOUS MONONUCLEOSIS

In the ordinary case of infectious mononucleosis, there should be little difficulty in reaching the diagnosis. The patient, who in the majority of cases is a male below thirty years of age, complains of headache, tiredness and sore throat, perhaps with pain or stiffness in the neck. Physical examination shows a variable degree of fever, congestion of the pharynx and slight to moderate enlargement of the cervical lymph nodes. In many cases the axillary and inguinal nodes are also swollen, and in about 50 per cent of cases the edge of the spleen can be felt an inch or so below the costal margin. As a rule, when the patient first seeks medical advice the leucocyte count is between 10,000 and 20,000. Examination of stained blood films shows that 60 to 90 per cent of the white cells are lymphocytes, and that the great majority of these lymphocytes are abnormally large cells with coarse, often indented or lobulated nuclei and vacuolated basophilic cytoplasm. These cells, which are often referred to as "mononucleosis cells" have been well described by Downey.[5]

The serum of a patient with infectious mononucleosis yields a strongly positive Paul-Bunnell test; that is, it agglutinates sheep's red corpuscles even when greatly diluted. Agglutinins for sheep's red cells may also be found in the blood of normal persons and in the blood of patients who have received injections of horse serum, but these agglutinins can be differentiated from the agglutinins of infectious mononucleosis by absorption tests with guinea-pig kidney tissue and beef erythrocytes (*v. inf.*). Rarely does the patient with infectious mononucleosis appear acutely ill. There is usually complete symptomatic recovery and disappearance of leucocytosis within ten or fourteen days, but the abnormal lymphocytes may be found in the blood for many weeks and the Paul-Bunnell test may be positive for months.

While this is the usual picture in infectious mononucleosis, variations occur both in the clinical and hæmatological features. The temperature may range under 100° during the whole course of the case or it may reach 104°. The fever may persist for several weeks, or it may be present only during the first few days of the illness. Congestion and soreness of the throat may be absent or there may be severe membranous pharyngitis. The cervical lymph nodes may be greatly enlarged, even in the absence of faucial inflammation, or they may be barely palpable. In some cases, such as the one here reported, the cervical or axillary nodes cannot be felt. A few patients have shown great enlargement of the spleen and this enlargement has persisted for years (Heck). Skin rashes,

urticarial or rubelliform, are not particularly rare, and jaundice has been noted in a number of cases. The occurrence of severe meningeal symptoms with an increased cell count in the spinal fluid has been reported (Thelander and Shaw[9]), and in a number of other cases, including one of ours (Table II, Case 6), headache and stiffness of the neck were prominent symptoms but spinal puncture yielded normal fluid. A febrile type of the disease is described, in which lymph node enlargement and the characteristic changes in the blood and serum do not appear until several weeks after the onset of pyrexia. Also described is a type in which abdominal pain, leucocytosis and fever in the early days of the illness, suggest a diagnosis of acute appendicitis or other inflammatory intra-abdominal lesion.

TABLE II.

THIRTEEN CASES OF INFECTIOUS MONONUCLEOSIS

Case	*Age*	*Sex*	*Enlarged lymph nodes*	*Enlarged spleen*	*Maximum temperature*	*Maximum leucocyte count*	*Maximum percentage lymphocytes*	*Paul-Bunnell Test*
1	25	M	Yes	No	102.0	22,050	90.0	
2	24	M	Yes	Yes	101.5	13,900	69.0	
3	34	M	Yes	Yes	103.0	21,000	87.0	1 in 400
4	28	M	Yes	No	101.0	9,600	88.0	1 in 400
5	19	M	Yes	Yes	101.0	28,000	87.0	
6	18	M	Yes	No	104.0	14,000	66.0	1 in 1,000+
7	18	M	Yes	No	101.5	13,500	71.5	1 in 1,000+
8	25	M	Yes	Doubtful	103.5	12,700	86.0	1 in 800
9	22	M	Yes	No	103.0	14,000	77.0	1 in 1,000+
10	20	M	No ?inguinal	Yes	99.2	18,800	77.5	1 in 800
11	17	F	Yes	Yes	99.4	10,000	51.0	1 in 600
12	25	M	Yes	Doubtful	99.5	11,200	55.5	1 in 100
13	17	F	Yes	No	Normal	12,900	69.5	1 in 600

The hæmatological features of infectious mononucleosis also vary, the only constant finding being the presence of abnormal lymphocytes of Downey's types I or II in the blood. Thus the total white cell count often ranges outside the usual figures of 10,000 to 20,000. Counts as high as 60,000 and as low as 1,500 have been recorded. Schmedheiny reported a total count of 2,000 with 90 per cent mononuclear cells on the twelfth day of the disease (Heck[5]), but in most of these cases leucopenia has been present only in the early stages and by the fifth or sixth day the count has risen to 9,000 or higher. It is not surprising that in some of those cases of infectious mononucleosis in which severe pharyngitis and leucopenia were associated, the first diagnosis was agranulocytosis. Characteristically, stem-cells or "blast-cells" are not to be found in the blood in infectious mononucleosis, and it is this feature, together with the absence of anæmia and the absence of thrombopenia, which distinguishes the disease from acute leukæmia. In exceptional cases, however, immature cells of Downey's type III and even true leukoblasts may be present in sufficient numbers to suggest that the reaction is of leukæmic nature.

In our series of cases the lowest leucocyte count at the height of the disease was 9,600 and the highest 28,000. The lowest lymphocyte percentage at the same stage was 51 and the highest 90 (Table II). In two of these cases (No. 1 and 6) the leucocyte counts were normal when the patients were admitted to hospital, and leucocytosis did not appear until the sixth day. In one clinically typical case (No. 8) the blood film showed some immature cells with leukæmic characters, but the Paul-Bunnell test was strongly positive and the patient made a good recovery. The clinical and hæmatological features in thirteen cases of infectious mononucleosis studied in St. Michael's Hospital during the past few years are shown in Table II.

DIFFERENTIAL DIAGNOSIS

As the clinical picture of infectious mononucleosis may be indefinite or may simulate that of other more serious conditions, much attention has been paid to the morphology of the so-called "mononucleosis cells" and to the diagnostic significance of the Paul-Bunnell test. We are satisfied, from our own observations, that cells indistinguishable from mononucleosis cells may be found in the blood in cases of lymphatic leukæmia, and that such cells may occasionally be seen in films from patients suffering from

various acute or chronic infections unassociated with lymphocytosis. Glanzmann has drawn attention to the similarity of the blood pictures, and sometimes of the clinical pictures, in infectious mononucleosis and German measles. Josephs[6] states that cells similar in mononucleosis cells may be found in the blood in certain cases of pertussis. Riley, studying an epidemic of influenza which occurred in Baltimore in 1931, found that in many of the children the acute phase of the infection was followed by general enlargement of the lymph nodes and the appearance of a blood picture indistinguishable from infectious mononucleosis (Josephs). Downey and Stasney[4] reported the same finding in one case of agranulocytosis and in one case of septicæmia, and Demanche[3] found blood changes similar to those of infectious mononucleosis in diphtheria, German measles, measles with lymph node enlargement, mild cases of typhoid fever and infectious jaundice. It is true that a worker trained in hæmatology will rarely have any difficulty in distinguishing infectious mononucleosis from leukæmia or from other diseases associated with lymphocytosis, but as such difficulty does occasionally arise it is important to enquire into the diagnostic reliability of the Paul-Bunnell test.

THE PAUL-BUNNELL TEST

Since about 1927 it has been known that the serum of a great many healthy people has the power of agglutinating sheep's red corpuscles and that this power is greatly increased after an injection of horse serum, particularly if the injection is followed by serum sickness. In 1932 Paul and Bunnell[8] found that there is a very much greater concentration of agglutinins for sheep's red cells in the serum of patients with infectious mononucleosis than in the serum of healthy persons or of persons who have had injections of horse serum, and this observation has been confirmed by a long series of reports. These reports indicate that if a sample of serum agglutinates sheep's red cells in dilutions higher than 1 in 200, the probability is that the patient has infectious mononucleosis, unless he is suffering from serum sickness or unless he has recently passed through an attack of serum sickness. However, as in some cases of infectious mononucleosis the sheep's cell-agglutinin titre of the serum remains below 1 in 200, and as in the serum of some healthy individuals this titre may be above 1 in 200, it is clear that the simple or presumptive Paul-Bunnell test may yield inconclusive results. Fortunately it is possible to distinguish between the sheep-cell agglutinins of normal serum, the sheep-cell agglutinins of serum sickness and the sheep-cell agglutinins of infectious mononucleosis, by absorption tests, using a suspension of guinea-pig kidney tissue and a suspension of beef erythrocytes. The effects of these antigens on the three types of agglutinins are shown in Table III.

TABLE III.

QUALITATIVE PAUL-BUNNELL TESTS

	Serum treated with suspension of guinea-pig kidney tissue	*Serum treated with suspension of beef erythrocytes*
Anti-sheep agglutinins of normal serum.	Completely or almost completely absorbed (90 to 100 per cent)	Absorbed only partially if at all (0 to 75 per cent. Average 35 per cent)
Anti-sheep agglutinins produced by serum injection	Completely or almost completely absorbed (90 to 100 per cent)	Completely or almost completely absorbed (90 to 100 per cent)
Anti-sheep agglutinins of infectious mononucleosis	Only partially absorbed (50 to 75 per cent)	Completely or almost completely absorbed (90 to 100 per cent)

The Paul-Bunnell test may be carried out in a series of small test tubes, as in Davidsohn's method or on a glass slide or plate, according to the technique devised by Straus. In our work we have adopted the Straus technique, as in this way the test can be done rapidly and the end-point of agglutination is easily determined under the low power of the microscope. The patient's serum is inactivated by heating in a water bath at 56° C. for twenty minutes. Serum dilutions of 1 in 10, 1 in 50, 1 in 100, 1 in 200, 1 in 400, 1 in 600, 1 in 800 and 1 in 1,000 are then made with normal saline solution. Using a capillary pipette, three drops of each of these serum dilutions are placed in separate one-inch squares marked on a sheet of plate glass with a diamond or grease pencil and, to serve as a negative control, three drops of saline solution are placed in another square. To each dilution of serum and to the saline solution control is then added one drop of a 2 per cent saline suspension of washed sheep's red cells. The cells and fluid in each square are thoroughly mixed and the plate is gently rocked for ten minutes. In a strongly positive test, there is complete agglutination of the red cells in the lower serum dilutions, which then show large bright red clumps floating in clear fluid. In the higher dilutions agglutination is incomplete and the fluid shows only a granular appearance. The end-point of agglutination, as determined under the low power of the microscope, is as a rule one dilution

higher than the end-point as determined with the naked eye.

The antigens for qualitative or absorption tests are prepared as follows. A guinea-pig's kidneys are minced with scissors, washed repeatedly in saline solution until the washings are free from blood, and mashed into a fine pulp. A 20 per cent saline suspension of the pulped tissue is made, placed in a test tube and boiled in a water bath for one hour. At the end of this time the loss by evaporation is made up with distilled water. The beef cell antigen is made by suspending one volume of washed and packed beef red cells in four volumes of normal saline solution, boiling the suspension for one hour in a water bath and making up any loss by evaporation with distilled water. Absorption tests are done by placing 0.4 c.c. of each antigen in small tubes, adding 0.1 c.c. of inactivated serum to each tube and allowing the mixtures to stand for one hour at room temperature, with frequent shakings. At the end of this time the tubes are centrifuged at high speed and the supernatant fluid, which represents a serum dilution of 1 in 5, is drawn off with a capillary pipette. Further serum dilutions are then prepared, and mixtures of these dilutions and the sheep's cells suspension are made on a glass plate, as for the presumptive test. The particles of tissue in the kidney antigen must not be too large to enter a 1 c.c. pipette, and both antigens should be shaken thoroughly immediately before withdrawing samples for the absorption tests.

We have done Paul-Bunnell tests by the Straus method on 400 unselected "control" sera taken from specimens of blood sent to the laboratory for Kahn and Laughlen tests, as well as on 10 sera from patients with infectious mononucleosis (Table IV). Six, of 1.5 per cent, of the controls showed agglutination of the sheep's cells in dilutions greater than 1 in 50, and these sera were further investigated by means of qualitative or absorption tests (Table V). Absorption tests were also done in 10 of our 13 cases of infectious mononucleosis (Table VI).

TABLE IV.

PAUL-BUNNELL TESTS—STRAUS METHOD

	Sera tested	*Negative*	*Positive*							
			1 in 10	*1 in 50*	*1 in 100*	*1 in 200*	*1 in 400*	*1 in 600*	*1 in 800*	*1 in 1,000+*
Controls.....	400	216	168	10	2	3	1	0	0	0
		98.25%								
Infectious mononucleosis	10	0	0	0	1 (Case 12, Table II)	0	2	2	2	3

TABLE V.

QUALITATIVE P.-B. TESTS ON CONTROL SERA YIELDING TITRES HIGHER THAN 1 IN 50

Serum	*Titre before absorption*	*Titre after absorption with kidney antigen*	*Titre after absorption with beef-cell antigen*	*Results indicative of*		
				Mononucleosis antibodies	*Serum sickness antibodies*	*Normal antibodies*
A	1 in 100	0	0	No	Yes (No information as to serum injection)	No
B	1 in 100	0	1 in 80	No	No	Yes
C	1 in 200	0	1 in 50	No	No	Yes
D	1 in 200	0	1 in 200	No	No	Yes
E	1 in 400	0	0	No	Yes (A.T.S. injection three months previously)	No
F	1 in 320	1 in 40	1 in 320	No	No	Yes

TABLE VI.

ABSORPTION TESTS ON FOUR CASES OF INFECTIOUS MONONUCLEOSIS

Case	*Titre before absorption*	*Titre after absorption kidney antigen*	*Titre after absorption beef-cell antigen*	*Remarks*
10	1 in 800 1 in 200 1 in 10	.... 1 in 10	 0	Mononucleosis reaction.
11	1 in 600	1 in 400	0	Mononucleosis reaction.
13	1 in 600	1 in 400	0	Mononucleosis reaction.
12	1 in 10 1 in 100 1 in 10	.... 1 in 5 1 in 5	.... 0 1 in 5	Weak mononucleosis reaction. Case clinically typical.

It is important to note that while in infectious mononucleosis the Paul-Bunnell test is usually strongly positive by the time the patient seeks medical advice, it may be negative in the early stages of the illness even when the clinical picture is well developed. In two of our cases (Table II, Nos. 6 and 12) the sheep's cell agglutinin titre of the serum did not rise above 1 in 10 until the sixth hospital day. The heterophile antibodies of infectious mononucleosis may be present in the serum long after all symptoms have disappeared. In eight cases studied by Davidsohn,[2] the number of days between the onset of the illness and the first appearance of a sheep's-cell agglutinin titre below 1 in 56, varied from 50 to 296, the average period being 119 days. In one of our cases, however, the titre dropped from 1 in 400 to 1 in 20 in 16 days. In another the titre was 1 in 800 on the fifth day, 1 in 200 on the thirtieth day and 1 in 10 on the fifty-first day. In a third case the titre dropped from 1 in 100 to 1 in 10 in eight days.

SUMMARY

Our experience with the Straus modification of the Paul-Bunnell test has been that 394 out of 400 control sera failed to agglutinate the sheep's red cells in dilutions higher than 1 in 50, whereas in 9 out of 10 cases of infectious mononucleosis the agglutinin titre of the serum was 1 in 400 or higher. However, as in one of the ten cases of infectious mononucleosis the titre did not exceed 1 in 100, and as in six of the four hundred controls the titre reached or exceeded this level, it is clear that a case should not be classified as one of infectious mononucleosis on the basis of the simple or presumptive Paul-Bunnell test. In all of our cases, absorption tests have served to distinguish the sheep's-cell agglutinins of infectious mononucleosis from similar agglutinins which may be present in the serum in other conditions.

CONCLUSIONS

1. Characteristically, a patient with infectious mononucleosis shows fever, pharyngitis, enlargement of the cervical lymph nodes, leucocytosis with a high percentage of abnormal lymphocytes in the blood and a positive Paul-Bunnell test.

2. In exceptional cases the picture is atypical. Fever may have disappeared by the time the patient seeks medical advice. There may be no pharyngeal inflammation. The lymph nodes may not be noticeably enlarged. The total leucocyte count may be normal or subnormal in the early stages of the disease, and the percentage of lymphocytes may remain below 60 during the course of the infection. Infectious mononucleosis is a pleomorphic disease which may simulate tonsillitis, mumps, German measles, diphtheria, Vincent's angina, agranulocytic angina, leukæmia, encephalitis, meningitis, thrombopenic purpura, catarrhal jaundice or acute appendicitis.

3. A constant feature of infectious mononucleosis is the presence in the blood of large numbers of abnormal lymphocytes, so-called "mononucleosis cells", but morphologically indistinguishable cells may occasionally be found in lymphatic leukæmia and as well as in various infections associated with lymphocytosis.

4. The presumptive Paul-Bunnell test is an unreliable diagnostic method. It is true that in the majority of cases of infectious mononucleosis the sheep's-cell agglutinin titre of the serum exceeds 1 in 200 whereas in other conditions the titre is usually below 1 in 100, but low titres in infectious mononucleosis and high titres in other conditions are not rare.

5. In our experience, qualitative or absorption tests with kidney tissue and beef-cell antigens serve to distinguish the sheep's-cell agglutinins of infectious mononucleosis from similar agglutinins which may be present in the serum in other conditions.

Our thanks are due to Miss Mercedes Lonergan who is responsible for the serological work reported in this paper.

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FATIGUE, REST AND EXERCISE*

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IF a single living muscle is excised and stimulated by an electric current it can be made to contract. If the stimulation is repeated often enough the contractions will become more and more feeble and finally cease. The muscle is said to be fatigued. The energy for contraction was supplied by the conversion of glycogen into lactic acid. The complete fatigue is due to the fact that the hydrogen-ion concentration has risen to such a point that no more glycogen can be converted into lactic acid. During rest, with an adequate supply of oxygen, sugar, and bases to replenish the alkali reserve, the lactic acid is reconverted into glycogen and recovery is soon complete. No analogous production of complete muscle fatigue ever occurs in the human being and yet the symptom of fatigue is often considered and treated in the light of this simple experiment. An additional factor is often postulated, namely, that the blood supply is inadequate in that it may contain some toxic agent, as in hyperthyroidism or be deficient qualitatively, as in pernicious anæmia. Often that is true.

If we stimulate the excised muscle by way of its nerve in the same fashion, we find that the same phenomenon occurs, namely, that after a few stimulations the muscle will stop contracting. However, if we at once change the stimulation from the nerve to the muscle, the muscle will again contract and continues until entirely fatigued. This shows that the nerve fibres fatigued before the muscle. If, in a third instance, the stimulus for muscle contraction is done by the mind through the nerve path to the muscle, we find that the subject of the experiment is able to keep up voluntary contraction of the muscle to a point at which he describes complete fatigue. He means that he is unable to make a voluntary effort of *will* sufficiently strong to contract the muscle. If, at this moment, the nerve supplying that muscle is then stimulated, the muscle will contract until the nerve fibres are exhausted and immediately further stimulation of the muscle will show response to stimulation to a further point. Thus, the onset of fatigue is earliest in the mind, next in the nerve fibres themselves and finally in the muscle. We see, therefore, that the contraction of a muscle, *i.e.*, a certain form of energy production or behaviour is limited by the ability of the subject to bear the cerebral distress of making an effort of *will* against increasingly strong, disagreeable painful sensory impulses. This is normal functional fatigue. Obviously, the quantity and quality of the blood to the parts must be adequate. A poorer quality of the blood, either from a deficient supply of normal materials as in heart failure or in deficiencies such as myxœdema, or because of the addition of toxic materials, as in active tuberculosis, will greatly reduce the time required to produce the syndrome called fatigue. This is organic fatigue.

Normal functional fatigue can properly be designated as the sensation and general experience and behaviour of the athlete after physical endeavour. This might be called "athletic fatigue" and can apply to ordinary fatigue or to fatigue in average persons who have only relative perfection of the integration of function, the perfection of integration of function coming only with athletic training. The state of the perfection depends on the life led by the individual.

In extreme athletic fatigue, one sees the fatigue of the mind, nerve paths, muscles, etc. It is impossible to say what part fails first, because the whole organization breaks down together and the point at which it breaks down is called the maximum production of energy of which that individual is capable. It is the purpose of an athlete's training to build up the efficiency of the various systems individually and also co-operatively. This perfects integration of chemical and physical functions and implies the proper inhibition of unimportant activities. Final physical exhaustion is reached when the cerebral distress from peripheral stimuli becomes so great that the individual is unable to initiate any voluntary effort further. Athletic training, therefore, enables, first, the best possible integration of all physical and chemical processes in the various systems so as to delay the onset of

* This is the successful Myers Memorial Essay for 1941.

extreme discomfort, and, finally, the training of the mind to stand increasing discomfort up to the final point which we call the "capacity" of that individual. This is not to say that weakening of the mind is the limiting factor in the full psychomotor power, but that that particular individual has reached the limit of his mental strength at that degree of disagreeable, sensory bombardment due to the increasing hydrogen-ion concentration and his diminishing supplies of raw materials, sugar and various salts. Thus, the mind is the first threshold of fatigue. As the pace and the time increase, the sensory barrage reaches and finally breaks the *will* of that person in order to save him from a disintegration of function and structural damage.

Organic Fatigue

The fatigue in organic disease is presumably caused by toxæmia. In addition to the diseased tissues involved in energy production, toxic agents alter cellular chemical processes, producing inadequacy in the signalling mechanism from faulty hormones or disordered function of the autonomic nervous system. The fatigue is not necessarily present until the tissues are being used and is thus in some respects comparable to that felt by an athlete approaching the limit of his capacity. The discomfort will be slightly different, however, since particular toxins will often have a particular selective effect. For instance it may have its maximum effect on muscle fibre or on nerve tissue or on the liver or on the brain cells, though all tissues will be affected. The fatigue of organic disease is banished to a more less extent by inactivity and increases with activity and is felt later in the day. Organic fatigue is an efferent difficulty, that is to say, there is resistance to motor stimuli, probably at the neuromuscular junctions. At the same time, there is increased afferent facility with heightened irritability of sensory stimuli. This decreasing resistance to sensory stimuli brings about cerebral distress earlier and has a biological object in the preservation of the individual. The break in the continuity of the production of energy begins peripherally, but the continual perception of uncomfortable stimuli finally fatigues the mind and the patient becomes irritable, depressed, and shows a diminution in his powers of concentration. Inactivity, *i.e.*, rest, by reducing the number of peripheral stimuli will allow these effects to pass off. But the constant repetition will finally induce what we call "habit" and this occurs on the afferent as well as the efferent side. Once a habit has been induced, the imprint remains for ever, growing fainter with the passage of time. Any future fatigue, whether organic or functional, may reveal those imprints in that habit pathway or pattern. Thus the previous habit of pain from the region of previous inflammation or other disease may appear in an episode of functional fatigue. The pain of duodenal ulcer from muscular spasm there, may reappear when that individual is functionally fatigued from psychological causes, a habit of reflex spasm having been established when actual ulceration was present on former occasions. Now, without the ulceration, but merely because of the facility of afferent and efferent stimuli in that area, the fatigue phenomena are increased during normal usage of that part. Constant or repeated perception of afferent impulses increases the acuteness and skill of recognition of those impulses and the shades of quality changes in those afferent impulses increase enormously with the practice of that appreciation.

Functional Fatigue

Functional fatigue begins centrally and extends peripherally. It is made worse by inactivity (rest) and is therefore most severely felt in the early part of the day and wears off as effort is made by deliberate action or necessity. The effort of *will* to initiate an effort of a physical or mental kind is great. The great inhibiting influence is a lack of desire or wish to initiate an effort.

In 1935 Norman Johnson in *Minnesota Medicine* (Vol. 18, page 531) published an excellent article on "Non-organic Causes of Fatigue" from which I freely quote. He quotes Capt. Hadfield of the British Army, "In the production of energy we are motivated by two forces. First by *impulse* (or desire) which is the stronger, and secondly by the *will*. Man gets his superhuman strength when his instinct or impulse violently urges some policy and his *will* gives complete and unqualified approval." When this is the case, no fatigue sets in, except the athletic exhaustion above referred to. Postponement of the cessation of energy production can be brought about by adding the nerve stimulation in order to augment the *will* power by some sort of suggestion. This is frequently used, such as the exhortations of the cox in the rowing crew, the cheering of a crowd for encouragement or by using some rhythmical, musi-

cal stimulation as in the dance and the army band. Conversely, earlier exhaustion, or a diminishing of the ability to stand the cerebral distress and exercise or "complete and utter fatigue is brought about when impulse or instinct strongly dictates a policy and the *will* violently disapproves." This is conflict. "In emergencies, one's reasoning powers move too slowly, and most of us revert to instinctive reactions of fear, anger, hate, jealousy, pride, greed, worry, anxiety, disappointment, self-consciousness, self-pity, despair, etc." These have tremendous powers for inhibiting our automatic machinery and bringing on fatigue symptoms. The subtle influences of fear in all its forms and grades are not easily analyzed. "The important point to remember is that our machinery is geared directly to our emotions." As mentioned above, superhuman energy is seen in action when our emotions coincide with our will. Where these are not in strict harmony, functional fatigue sets in to thwart the object of the weaker one. For example, "a person has functional fatigue when he forces himself to perform some task which he heartily dislikes, whereas five times the energy is expended on some pleasant task which results in only transitory fatigue" (Hadfield) of a different kind. "Some persons have been educated to put an emphasis on results, rather than giving their best effort to the performance and to let the result happen. If the best is done, automatically you will produce the best result of which you are capable. Work should be done without getting mentally in a hurry."

"Functional fatigue is also caused by the refusal to accept an adverse fact. Most basic of all is probably the fallacy of the conviction of our individual entity being the centre around which all the rest of the world revolves. This produces 90 per cent of the disagreeable emotional upheavals of an individual and of mankind. The most enjoyable experiences have come at a time when one's attention was riveted on some consuming interest, on some goal for which you strive, or in fact anything except your relative position in life." The symptoms of functional fatigue are due to the inco-ordination between the various systems and the imbalance between the sympathetic and the parasympathetic portions of the autonomic nervous system. When slight, the actual biochemical changes are not measurable by our methods and yet some of the biochemical changes with emotion are known. When functional fatigue is chronic and more severe, biochemical changes are demonstrable; changes in the basal metabolic rate, changes in the sugar metabolism, changes in the blood pressure, changes in the pulse rate, and also changes in the heat control mechanism. Thus in severe functional disturbances, some of these changes in metabolic processes may be severe and be mistaken for the changes often seen in organic disease. Even in mild psychoneurotics, earnest attempts are made by medication or surgical therapy, to rectify these changes in function without success. This lack of success is inevitable because these changes are the effect and not the causes of the disturbance. Frequently, the measures taken to alter these effects merely cause further upsets in function, together with the functional upset that comes from chronic disappointment. Most commonly, the disorganization which brings on functional fatigue and due to disorders of the autonomic machinery, is an acquired state and can easily be mistaken for organic fatigue. Psychological causes such as boredom, disuse, lack of discipline, and chronic fear connected with the social state, with the economic state and with physical health are common. The neurasthenic is a personality who has a poorly functioning nervous system from birth and these are the people who always have suffered from an uncomfortable functioning of their bodily machinery brought out more easily and more violently under conditions of stress and strain, that is, when they attempt automatically to adjust to some change in the environment which is too great for them. These are the patients who are always complaining; that is to say, they always have symptoms.

An important group of patients in whom functional fatigue is of particular interest are those who have inherent defects of vegetative function. These are the migraine personalities with its various equivalents such as asthma, eczema, angioneurotic œdema, urticaria, mucous colitis, cyclic vomiting of children, and certain types of dysmenorrhœa. Functional fatigue, manifesting itself always through disturbed vegetative function, will of necessity bring these defects out in high relief and the appreciation and treatment of the additional psychogenic factors are fundamental.

REST AND EXERCISE

Rest from athletic fatigue means the total inactivity of the body and mind for a period which has definite limits. In organic fatigue,

namely, that due to toxic states due to infection, degeneration, or new growth, or to poisoning from endogenous sources, rest is also that of an inactivity of the part and of the whole patient until the source of the intoxicating material is removed and the results of the intoxication are repaired and the metabolism of the cells is restored to normal. As soon as the toxins are removed or prevented from forming, the convalescent state begins. This rehabilitation period, called the convalescent state, is a period of change and requires a nice adjustment between rest and increasing exercise of the part and the whole of the patient. The fact that the whole individual is taking part in the convalescence is often overlooked. Graduated use of the various faculties and physical properties of that individual have to be used in greater frequency and in increasing difficulty. This is analogous to the early part of an athlete's training. During the convalescent stage from infection or other toxæmias, many of the psychoneurotic states originate in healthy people. The previous toxic state has resulted in a disintegration of function of the various systems and of the cells in each system and, following the removal of that toxæmia, *this* functional fatigue remains. The restoration of this liability to functional fatigue may well be met with the ordinary natural tendency of the individual to recover spontaneously. But, if the period of previous toxæmia has been prolonged, even those who have strong autonomic nervous systems and constitutional organization, as it is called, may yet require careful coaching in the re-education or exercise process to avoid the habitual functional fatigue symptoms which are necessarily and normally present at the beginning of the convalescent stage. It can thus be seen, too, that in long continued, chronic, organic disease and in suitable personalities, functional fatigue symptoms overtake and overshadow finally the organic symptoms. Frequently, however, the distinction between the organic symptoms and the functional fatigue symptoms is not clearly distinguished by those who come in contact with the patient. Therefore, there is a possibility that the whole complex clinical picture becomes a mixture of functional, that is to say secondary psychoneurotic, symptoms combined with the organic symptoms and the latter may fade in reality to the vanishing point. The onus having started with the organic disease, symptoms may still be thought to be treatable on the basis of the original organic lesion, but specific treatment directed towards the organic lesion will not, of course, have any effect on the secondary and now more urgent and possibly overwhelming symptoms of functional nervous disturbance.

The word "rest" is used rightly when applied to the fatigue of organic disease. Inactivity, however, is not restful for the organization that is suffering from functional fatigue, and becomes but an opportunity for deterioration. In functional nervous disorders, rest is only obtained by using all parts, including the mind and nervous system of the organism in the way that they were supposed to be used, beginning with a small amount and increasing the difficulty and the duration until a normal level of usage is arrived at. Together with this, frequent changes in the kind of energy production is the only way of producing a restful effect. Anxiety or fear and boredom (monotony) are the greatest producers of functional fatigue. The only method possible to remove fear and boredom is, first of all, that the patient and the doctor should be aware of their presence, to accept their positive reality and be willing to try to erase them. This sets in motion psychological and physiological constructive forces which are inherent in each individual. They are, of course, strongest in those who are endowed with a strong intellect and intelligence. The physiological benefits from clear understanding are enormous. Rest, therefore, consists of an alternation of activity with shortening periods of inactivity. Exercise is the initiation of different kinds of effort. This practice in *willing,* in the presence of understanding, does increase the strength of *will power.* The rapidity of recovery, therefore, depends mostly upon the previous habits of discipline in that patient.

Exercise consists in the repeated trials of the efficiency of the integration of that individual at the moment, the test requiring a more perfect integration than obtains at that time and, therefore, resulting in slight sensations of fatigue. This process of working the organization just beyond its level of efficient integration at the moment and giving rise to a suggestion of increased effort, whether mental or physical, is what we call education. By the repetition of this procedure in health, a greater production of energy will be found possible before inefficient integration takes place, with the important proviso that the experiments should not be too far apart. This is best illustrated by the

athletic illustration, namely, that in running a race of say, ten miles, the first effort should be half a mile, the second three-quarters of a mile, the third one mile, the fourth one and a half miles, etc., but the intervals between these extensions of time and distance will have to be carefully selected, for if the interval is too great the previous education involved in increasing the distance will have worn away. The word education has usually been applied to intellectual activities alone but the same principle holds good. Exercise also consists in the practice of varying co-ordination, as it is just as important to have perfect inhibitions as it is to have perfect stimulation.

The previous discipline of the patient in every sphere is seen frequently in organic disease. The more disciplined the patient has been previously, the longer will be delayed and less severe and elaborate may be the symptoms of the onset of organic fatigue. In this way more severe toxæmias, especially if started slowly, will be borne by the more disciplined patient. In them toxæmia may reach a high point before the patient will acknowledge fatigue. On the contrary, the undisciplined, emotionally uneducated patient has symptoms of fatigue from a slight organic lesion. He has been educated in easy disorganization.

Many somatic discomforts and signs are expressed by the word "fatigue" and those of functional are no less important than those of organic origin. Of the functional variety there are those due to abnormalities of vegetative function from mildly pathological psychological states—the commonest of which are fear and dissatisfaction. My concern here is to re-emphasize the truth that organic dysfunction, functional vegetative dysfunction, and psychogenic dysfunction are all on the same physiological footing and must be dealt with by the physiological method. They all give rise to symptoms difficult of distinction. The simple psychological analysis of an ill individual is not *more* important than the organic analysis—the point is that it is not *less* important. Its omission is unscientific and represents one of the serious flaws in the practice of the art of medicine today, particularly by specialists. Literally, hundreds of years of good health are lost by not taking time to do this. The natural history of the patient; as he has been born, as he has been reared and fed, as he has been acted upon by people's opinions, as he has been affected by religious, social and economic conditions, is equally important (neither more nor less) as the effect on him of pathogenic organisms or of degenerative changes in his tissue cells. Take nothing for granted. The absence of significant findings is quite as helpful as their presence and therefore our duty compels us to examine the private life and thoughts of patients just as carefully as we should do a rectal examination. Medically, one is not more private than the other.

Not until the organic or non-organic nature of fatigue symptoms are appreciated can the appropriate measures of correct rest or exercise be applied with understanding and wisdom.

PHYSIOLOGY OF SPINAL ANÆSTHESIA*

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THERE are few chapters in the history of Medicine in which there has been more misconception and controversy than in the case of spinal anæsthesia.

The confusion on this subject arose from its early clinical application without adequate physiological investigation. This state of affairs persisted because the management of the procedure was entrusted all too commonly to assistants with relatively little training in anæsthesia. In recent years the researches of laboratory workers and the clinical observations of competent anæsthetists have brought to light many facts unknown to the pioneers in this field. It is now known that in addition to loss of pain and motor functions, widespread changes of other nature are engendered. But while in the main these principles are understood, there is no settled opinion as to the exact sequence of the events which precipitate cardiovascular depression, some degree of which is present in most cases of spinal anæsthesia. There is certainly difference of opinion as to the relative importance of the several

* Read at the Seventy-second Annual Meeting of the Canadian Medical Association, Winnipeg, June 26, 1941.

changes which come under suspicion as offending in this respect. It is clear, in any case, that some understanding of the basic principles of this whole subject is essential to a sane projection of this valuable and perhaps indispensable anæsthetic measure.

Spinal anæsthesia is established by the injection of a local anæsthetic agent into the spinal subarachnoid space. The nerve roots at this point are extremely vulnerable. Loss of pain and motor function appear almost immediately. The number of segments involved depends upon the dosage used and upon certain other variable factors in the details of technique. Absorption from the subarachnoid space is known to be relatively rapid, so that the vital cerebral centres are exposed to the action of the anæsthetic agent. The amount of the drug reaching the blood stream varies with the dosage and the volume of the solution injected. Jones believed the drowsiness commonly observed in spinal anæsthesia to be a systemic effect of these toxic agents. Vomiting is frequently mentioned as being similarly caused. In this connection, however, it may be noted that in thoracic surgery, in which large dosage of procaine (up to 300 mg.) is used and high blocks established, vomiting is of rare occurrence. It is probable that in most instances, though by no means all, vomiting is a reflex and is due to intra-abdominal manipulations.

Observers, such as Jones[1] and Nowak,[2] believed circulatory upset to be due to this absorption factor. It has been demonstrated, however, that procaine, in amounts comparable to those used in spinal anæsthesia, may be injected directly into the blood stream without effecting degrees of circulatory depression corresponding to those commonly encountered in spinal anæsthesia. It is reasonable, of course, to assume that the injection of drugs of such toxic nature into the human body must have deleterious effects. Research workers and anæsthetists alike, however, appear to be in agreement that this absorption factor is not the principal cause of the circulatory disturbances of spinal anæsthesia.

In satisfactory spinal blocks for major procedures, some degree of intercostal paralysis, as well as paralysis of the abdominal musculature, results. In establishing complete abdominal anæsthesia, 4th or even 3rd thoracic levels are necessary. Compensatory diaphragmatic action or overactivity of the intact intercostal musculature to any appreciable degree is rarely evident clinically unless oxygen want becomes acute. There may be interference, also, with diaphragmatic function without definite clinical evidence of phrenic nerve involvement. Under these circumstances impairment of pulmonary ventilation is inevitable. The cyanosis commonly observed in spinal anæsthesia may thus be explained. It is believed, too, that in eliminating intercostal activity to the degree necessary for high spinal block, one of the supports of the circulation is removed.

The loss of tone of the general musculature in which is embedded a considerable portion of the arteriolar-capillary-venous side of the circulation, by removing some degree of support to the wall of these vessels, sets up venous stagnation, thereby slowing the return of blood to the heart. In wide blocks this may be an important consideration.

Some of the anæsthetic agent may escape absorption in the spinal area and by dispersion reach the brain stem or the brain itself. There is the possibility, also, that some of the drug in the blood stream may be excreted by the choroid plexus into the cerebrospinal fluid in that area. Abducens paralysis is best explained, perhaps, by this deduction. Some degree of depression of the vital cerebral centres from these causes may, therefore, be assumed. Burstein has shown also that in total spinal anæsthesia in dogs, the mechanism regulating blood pressure during changes in posture is disturbed.

Physiological section of the preganglionic fibres of the sympathetic nervous system effects widespread changes in the human organism. Vasomotor paralysis in spinal anæsthesia has long been recognized and has been cited frequently as a cause of circulatory upset. Massive pooling of the blood in the splanchnic vessels is not evident clinically. Nor is there much evidence that there is appreciable enlargement of the liver or spleen in man, although such findings have been reported in animals. There can be little doubt, however, that there is a considerable increase in the amount of blood held in the skin, the general musculature, the liver and spleen, so that the enlargement of the vascular tree spoken of by Co-Tui is probably true. Co-Tui[3] states that an immediate severe drop in blood pressure occurs in dogs, which is followed by an almost

instantaneous rise to normal levels, the latter effect being due, he believes, to compensatory vasoconstrictor activity in the unaffected regions of the body. Ferguson and North[4] have shown, however, that section of all the splanchnic nerves in animals does not produce fall in blood pressure comparable to that associated with spinal anæsthesia. Further, Smith *et al.*[5] appear to have demonstrated that the arteriolar system possesses some autonomy and is independent of vasomotor activity. It is certain, nevertheless, that vasomotor changes in some way contribute something to the production of circulatory depression.

The innervation of the adrenal bodies may be completely or partially severed in spinal anæsthesia. If the view is held that these glands act in emergency situations only, it could be pointed out that the cardiovascular crises of spinal anæsthesia constitute just such an emergency. In this connection, it is interesting that the use of sympathomimetic drugs offers one of the most efficacious remedial measures in this situation.

In some instances of spinal anæsthesia a portion of the anæsthetic drug may reach the upper thoracic region and so cut off the cardiac accelerator nerves. When this is the case the cardiac action of the vagus is left unopposed. Bradycardia is a common observation in spinal block. The fact that a very small dosage of procaine is adequate for thermal skin test may be quoted as evidence that sympathetic fibres in general are vulnerable to weak concentrations of the drug in the spinal fluid.

Contraction of the small bowel and increased peristaltic activity are explained by unopposed vagal action when the dilator muscles become deprived of their innervation. The sacral portion of the parasympathetic nervous system is involved in most techniques with consequent loss of tone in the anal sphincter.

Other processes, no doubt, take place in the course of a spinal anæsthesia. We may reasonably hope that future researches in this subject will explain some of the perplexing phenomena at present associated with this procedure.

It is evident from a consideration of the above points that in the process of establishing the desired loss of pain and motor functions a highly complex series of changes in body mechanism is brought into being. Some of these are, no doubt, of small significance. Others, such as those leading to impairment of circulatory efficiency, are of first importance. There is little doubt that a decrease in cardiac output of greater or lesser degree, with consequent reduction in the oxygen supply to vital centres, exists in all subarachnoid blocks. It appears that several factors contribute to this circulatory failure. The summation of these in some instances may be disastrous. Clinical experience suggests that a factor which is of first importance in this connection in one instance may be of only minor significance in another. For example, the absorption factor may be the predominating cause in individuals possessing some special sensitivity to the anæsthetic drug. It may be the vasomotor effects which offend, as when depression occurs following induction of low blocks with a small dosage. This situation is encountered sometimes in the aged, whose circulatory mechanism is unstable and inelastic. In other instances circulatory depression may be secondary to impairment of respiratory function. A sound interpretation, therefore, of the nature of the existing disturbance is helpful by pointing the way to appropriate remedial measures.

The anæsthetist armed with a knowledge of the physiological principles of spinal anæsthesia possesses the key, not only to the selection of patients, but also to their management. Persons with cardiovascular disease are not good risks. The aged, who are certain to have damage of this character, should be placed in this category. Patients suffering from anæmia are unsuitable because of impairment of the oxygen-carrying power of the blood. Spinal anæsthesia is not a good choice in the presence of surgical shock or hæmorrhage. It likewise should be used cautiously, if at all, in operations in which shock or considerable blood loss is anticipated. Animal experimentation confirms this view. The protective vasoconstrictor mechanism may operate less efficiently under spinal anæsthetic conditions, even if the arteriolar system should be independent of the vasoconstrictor nerves. Patients suffering from anoxæmia from any cause are obviously poor risks. The temptation to risk a reduced dosage should be resisted in all of these circumstances unless the surgical condition strongly indicates spinal anæsthetic measures.

With respect to patients in spinal anæsthetic shock, the obvious restorative measures consist in the administration of reliable vasopressor drugs, of intravenous fluids, and of oxygen.

Artificial respiration when indicated should be instituted at once. It is important that these measures be applied before their need becomes acute. Restorative measures of other nature appear to be of little value.

Few patients need be denied spinal anæsthesia when the benefits to be derived therefrom are plain. Constant care as to the choice of patient and scrupulous attention to all details of management are the safeguards against the pitfalls which lie in wait for the unwary.

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THE USE OF SYNTHETIC VITAMIN K SUBSTITUTES IN THE TREATMENT OF PROTHROMBIN DEFICIENCY*

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VITAMIN K

TWO previous papers[1, 2] have dealt with the hæmorrhagic tendency associated with prothrombin deficiency and its treatment with vitamin K and bile. This paper records our experiences with cases which have been treated by means of synthetic vitamin K substitutes. The cases under study were those which presented in the medical and surgical wards of the Montreal General Hospital during 1940, and the first half of 1941. For purposes of analysis the cases were divided into three groups.

1. Those patients with obstructive jaundice and prothrombin disturbance exhibiting a satisfactory response to K therapy.

2. Those with prothrombin disturbance associated for the most part with moderate to severe liver damage, who showed a variable response to vitamin K administration.

3. Those with hæmorrhagic tendency associated with neither jaundice nor prothrombin disturbance and where the hæmorrhage would probably not be influenced by vitamin K therapy.

METHODS

Prothrombin times were determined by Quick's method, which has become a familiar procedure in most laboratories.

The synthetic K substitutes which have been reported as active by mouth and also those which have been successful when administered intramuscularly and intravenously were used in the studies. The following preparations were used:

(*a*) 2- methyl -1, 4-naphthoquinone.
Dosage—1 to 2 mg. daily intramuscularly.
(*b*) 2- methyl -3 phytyl-1, 4-naphthohydroquinone.
Dosage—1 mg. daily intramuscularly.
(*c*) Propionyl derivative 2 methyl-1, 4-naphthohydroquinone.
Dosage—2 mg. daily intramuscularly.
(*d*) 2- methyl -1, 4-naphthohydroquinone diacetate.
Dosage—5 to 10 mg. daily intramuscularly.
(*e*) 2- methyl-1, 4-naphthohydroquinone disulphate.
Dosage—5 to 10 mg. daily intramuscularly.
(*f*) 4-amino - 2 methyl, naphthol hydrochloride.
Dosage—2 mg. daily intramuscularly or intravenously.

RESULTS

1. *Cases of obstructive jaundice treated with synthetic K preparations.*—This group is comprised of 3 cases of carcinoma of the pancreas; 2 with stones in the common duct; 4 with cholelithiasis; and one with carcinoma of the colon with obstruction of the common duct; one with carcinoma of the bile ducts; and one with obstructive jaundice of unknown etiology.

In all of these cases there was a disturbance of the prothrombin time and in every case the prothrombin time was restored to normal prior to operation. In no case was post-operative bleeding encountered.

All cases except two responded in 3 to 4 days to various drugs in the dosages already mentioned. One case on 2-methyl-3-phytyl-1, 4-naphthohydroquinone, 1 mg. intramuscularly, daily, required 8 days to produce a satisfactory response. The second case required 7 days before a satisfactory result was obtained. This patient was on a preparation of 2-methyl-1,

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Aided by the Blanche Hutchison Research Fund, Faculty of Medicine, McGill University.

4-naphthohydroquinone propionate, 2 mg. intramuscularly, daily.

Thirty-seven other cases of cholelithiasis and cholecystitis, with and without jaundice were treated with these preparations in spite of normal prothrombin times, and none showed post-operative bleeding. To this latter group may be added 2 cases of jaundice, one due to adenocarcinoma of the gall bladder, the other to adenocarcinoma of the common bile duct and ampulla of Vater. Neither case showed a prothrombin disturbance, despite which both were treated prophylactically.

2. *Cases showing prothrombin time disturbance and liver damage.*—In this second group there was one case of hepatomegaly with splenomegaly of undetermined etiology, three with cirrhosis of the liver, two of these with ascites and three cases with subacute yellow atrophy. One of the patients with acute yellow atrophy recovered, the other two died and the diagnosis was confirmed by post-mortem.

All were treated with one of the synthetic K preparations of known potency already mentioned. Many of these cases received relatively intense treatment and these cases showed a return of the prothrombin time to normal. In two of the cases of cirrhosis, the prothrombin time did not return completely to normal, suggesting that enough impairment of the liver existed to interfere with prothrombin production by the liver. In one case of subacute yellow atrophy the patient progressed into coma and the return of the prothrombin time to normal followed the clinical improvement to recovery. The complete restoration of the prothrombin time to normal cannot be considered due to K therapy alone.

In the two fatal cases of acute yellow atrophy the prothrombin times became gradually increased until death, in spite of adequate K therapy.

Similar cases showing no disturbance in prothrombin time are also worthy of note, these include two cases of catarrhal jaundice, one of hæmachromatosis, three of cirrhosis of the liver, two cases of mucous colitis and one of ulcerative colitis.

In addition three other cases have been included in this group because the conditions are known to give rise to disturbed prothrombin times, but are unrelated to obstructive jaundice or liver damage. They are briefly summarized.

One case of biliary fistula only revealed hæmorrhage on the 8th post-operative day following drainage of the common bile duct for acute cholecystitis. At this time the prothrombin time was found to be disturbed but the hæmorrhage was controlled and the prothrombin time returned to normal in 48 hours following adequate K therapy.

A second patient with extensive diverticulitis was admitted with severe hæmorrhage and a prothrombin time of 35 seconds. The hæmorrhage was controlled in 48 hours following the intramuscular administration of 5 mg. of 2-methyl-1, 4-naphthohydroquinone diacetate, four times per day.

A striking disturbance of prothrombin time (97 seconds) was discovered in a third patient suffering from carcinoma of the stomach with a history of continued vomiting over a period of four months. Hæmorrhage occurred on the 13th post-operative day, but was controlled by the intravenous injection of 2 mg. of 4-amino-2 methyl, naphthol hydrochloride on three occasions during a 24 hour period.

3. *Cases with hæmorrhagic tendency associated with neither jaundice nor prothrombin disturbance.*—A large number of cases with a hæmorrhagic tendency have been studied as a routine in the hospital and are presented in the accompanying Table. The occurrence of a disturbed prothrombin time in obstructive jaundice, liver damage, and certain gastrointestinal conditions is established and the response to vitamin K known. A certain amount of investigation in regard to other hæmorrhagic states has been prompted because of the possible application of K therapy to control hæmorrhage in these conditions.

The prothrombin-clotting times in a number of such conditions with an abnormal tendency to bleed are presented in Table I.

In a limited number of these cases vitamin K preparations have been used with no change in prothrombin times and no apparent effect in controlling the abnormal bleeding.

However it must be realized that hypoprothrombinæmia and hæmorrhagic diathesis may occur in many gastrointestinal conditions associated with a deficiency diet, loss of essential substances by vomiting, diarrhœa, unusual mucosal surface, etc.[3] Among these are peptic ulcer, gastric carcinoma, ulcerative colitis, diverticulitis, and others which under certain circumstances may develop prothrombin-time disturbances. When such disturbances occur the

TABLE I.

Cases	*Diagnosis*	*Prothrombin time in seconds (Quick)*
2	Acute glomerulo-nephritis ..	20, 22
3	Chronic glomerulo-nephritis with uræmia	21, 15, 19
7	Hæmophilia	25, 25, 23, 15, 21, 22, 25
2	Mucous colitis; ulcerative colitis	19, 15
2	Colliculitis	15, 15
1	Cerebral hæmorrhage	20
24	Adenoma of prostate, carcinoma of prostate[1] .	22, 22, 23, 24, 24, 25, 26, 16, 22, 24, 20, 24, 21, 15, 19, 15, 16, 18, 18, 20, 20, 21, 21, 20
6	Nasal hæmorrhage	16, 20, 26, 21, 15, 20
4	Fibroid uterus	17, 20, 21, 24
8	Gastric ulcer with hæmorrhage	17, 25, 26, 26, 20, 27, 17, 21
10	Duodenal ulcer with hæmorrhage	18, 18, 18, 18, 23, 25, 20, 20, 19, 19
6	Scurvy 2; purpura 2; aplastic anæmia 2	17, 22, 24, 22, 17, 19
1	Eales' disease (recurrent hæmorrhage into vitreous)	18
5	Carcinoma of sigmoid, colon and rectum	18, 18, 22, 22, 21
4	Gastric carcinoma	19, 20, 20, 22
3	Tuberculosis of lung, kidney	19, 19, 24
3	Diverticulitis	21, 21, 23
4	Chronic myelogenous leukæmia 2; acute leukæmia, lymphosarcoma	22, 24, 25, 23
1	Septicæmia	27
1	Renal calculus	16
1	Subacute gastritis	18
1	Post-operative tonsillar hæmorrhage	21
2	Chronic osteomyelitis	30, 19
2	Pernicious anæmia	22, 22
1	Renal tuberculosis	24
1	Bilateral cataract and diabetes	19
1	Splenomegaly	22
1	Schirrhus carcinoma of the breast	23
2	Bronchiectasis	25, 25
1	Tabes with gastric crisis (suspected cholecystitis)	20
2	Incomplete abortion	17, 20
3	Hyperplastic endometrium..	17, 19, 23
1	Adenomyosis uteri	25
2	Hæmatoma buttock	21, 20

hæmorrhagic diathesis may well be expected to respond to K therapy. However, in cases where the prothrombin time is normal, we feel that any associated hæmorrhage will not respond to vitamin K therapy.

DISCUSSION

Many authors have simultaneously reported the structure of an active antihæmorrhagic principle in alfalfa to be 2-methyl-3-phytyl-1, 4-naphthoquinone, and a number of related compounds have been synthesized and studied for vitamin K activity.[4, 5, 6]

Further reports have shown these synthetic compounds to be effective when taken orally and also when used by the intramuscular and intravenous routes.[7, 8, 9, 10, 11]

Of the preparations we have used, and the effective dosages as listed under methods the least active appears to be 2-methyl-3-phytyl-1, 4-naphthohydroquinone, and the most readily absorbed because of its solubility is the 4-amino-2-methyl naphthol hydrochloride. For the same reasons the latter is more effective when used intravenously. The advantages of the parenteral compounds are that they are effective without bile salts, produce no nausea or vomiting and have, so far, exhibited no toxic effects.

Whilst our main interest was to study the effectiveness of the compounds, the occurrence of a number of cases with liver damage enabled us to make certain observations. It is known that administration of vitamin K and synthetic compounds are less effective when the prothrombin deficiency is associated with liver damage.[12, 13, 14, 15, 16, 17]

In several cases the prothrombin returned to normal, but in others there was only a partial response. Some of the patients had ascites with congestion and œdema of the bowel, factors likely to interfere with absorption of the synthetic K if this has been given by the oral route.[18]

In these cases, however, the preparation was given parenterally and these results require some other explanation. The initial deficiency in prothrombin in part may have been due to impaired absorption, but sufficient functioning liver remained to utilize the synthetic compound in the restoration of the prothrombin to normal. Failure of the prothrombin time to return to normal may have been due to inadequate dosage under the existing conditions, or the liver was sufficiently damaged to interfere with a normal prothrombin concentration in the blood.

In three patients with acute yellow atrophy, the prothrombin time became further impaired as the patients entered coma and in two cases death. The progressive destruction of the liver was paralleled by a disturbance in the prothrombin time, suggesting that this test may have diagnostic and prognostic value as a liver function test in diseases of the liver. In a third case, as the clinical condition became critical the prothrombin time increased, and when recovery occurred the prothrombin time returned to normal. Therapy in this case was important in the clinical improvement although in no wise can

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it be considered a specific in bringing about recovery.

Observations on the group of cases having a hæmorrhagic diathesis unrelated to a deficiency in prothrombin corroborates observations of others that there is no reason or rationale for the administration of vitamin K or synthetic compounds to patients who show normal prothrombin times.

The synthetic vitamin K substitutes used in these studies were furnished through the kindness of Messrs. Ayerst, McKenna & Harrison, Limited, E. R. Squibb & Sons, and Parke, Davis & Company.

The patients studied were under the care of members of the staff of the Medical and Surgical Departments of the Montreal General Hospital, to whom the authors are indebted for the privilege of these studies.

We also wish to thank Miss J. Bowden and the Misses A. Durrell, J. MacIver and E. Peck for their valuable technical assistance.

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RÉSUMÉ

Les substituts synthétiques de la vitamine K ont été employés, 1° dans des cas d'ictère par obstruction avec troubles dans le rythme de la prothrombine; 2° dans des cas de troubles prothrombiniques avec lésions hépatiques, et 3° dans des cas de diathèse hémorragique sans ictère et sans troubles de la régulation de la prothrombine. Les premiers ont répondu de façon satisfaisante à la thérapeutique par la vitamine K synthétique. Les seconds ont répondu de façon moins constante. Les troisièmes n'ont été aucunement influencés. Les composés synthétiques peuvent agir aussi bien par la bouche que par les voies intraveineuses et intramusculaires. Le voie parentérale a cependant l'avantage d'être efficace sans sels biliaires ajoutés et elle ne provoque pas de nausées.

JEAN SAUCIER

THE INFLUENCE OF MENSTRUATION ON CARBOHYDRATE TOLERANCE IN DIABETES MELLITUS*

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DIABETES mellitus has long been known to exert a marked influence on menstruation and sexual function. Formerly amenorrhœa was quite common in diabetics and was frequently associated with an impairment of libido and sterility.[1] Similarly, in the male diabetic impotence and sterility were frequent findings. Anatomically, in female diabetics an atrophy of the uterus and ovaries has been reported,[2] which has been regarded as secondary to the diabetic condition. However, since the discovery of insulin and the resulting improvement in treatment such anatomical and physiological sexual abnormalities in diabetics have become infrequent.

Also, during the past 15 years a great deal of information regarding the relationship of the anterior pituitary gland to carbohydrate metabolism and diabetes mellitus has been accumulated. This work began with the important contributions of Houssay and his collaborators,[3, 4] who demonstrated that, in an animal made diabetic by pancreatectomy, hypophysectomy ameliorated the diabetic state, while, on the other hand, treatment with anterior puituitary extract aggravated it. Later it was shown that a normal animal with an intact pancreas became diabetic when treated with anterior pituitary extract. Furthermore, it has been demonstrated recently by Young,[5] Campbell and Best,[6] and Dohan and Lukens[7] that prolonged treatment of normal animals with anterior pituitary extract induces a diabetic state which persists even after discontinuation of the extract and remains permanent.

During the same period the relationship between the anterior pituitary and sexual function and menstruation has also been worked out in considerable detail. It has been satisfactorily shown that normal menstruation occurs only after œstrogen and corpus luteum hormones have acted upon the endometrium and that the elaboration of these hormones by the ovary is in turn controlled by gonadotropic hormones secreted by the anterior pituitary. Failure of

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the secretion of these gonadotropic hormones by the pituitary is followed by the cessation of the formation of œstrogens and progesterone by the ovary, resulting in amenorrhœa. It is also known that maturation of the ovum and ovulation, and therefore fertility, are controlled by the anterior pituitary.

In view of the above facts a study was undertaken to show whether menstruation had any effect on the carbohydrate tolerance of the diabetic female. A review of the literature suggests the probability of a moderate lowering of carbohydrate tolerance with menstruation. Von Noorden[8] made this observation years ago; he claimed that 20 per cent of diabetic females manifest a tendency to decreased carbohydrate tolerance during menstruation. In 1918 Harrop and Mosenthal[9] reported the case of a female in diabetic acidosis who, after showing some improvement, became much worse with the onset of menstruation and later died in diabetic coma during a menstrual period. Rosenbloom[10] observed a daily glycosuria of 10 to 22 gm. during menstruation in two females who ordinarily were free from glycosuria. Recently Peperkorn[11] reported two cases of diabetic acidosis occurring during menstruation. Although both of his patients improved, their condition became aggravated again at the following menstrual period. This author states that he has observed 14 cases in which the diabetes became worse during menstruation.

A similar, though less marked lowering of carbohydrate tolerance has also been noted in normal, non-diabetic women during menstruation. Heilig[12] investigated the glucose tolerance of a number of normal females during menstruation and in the intermenstruum. He found that in a large proportion of cases there was a marked impairment of carbohydrate tolerance on the first or second day of menstruation. His figures indicate that during the menstrual period the peak of the venous glucose curve was in some cases as much as 100 to 150 mg. per cent above the fasting level, that the drop to normal occurred in four to five hours, and that glycosuria was present. The fasting blood-sugar levels were investigated in a number of cases by Bloch and Bergel.[13] They found that the curve of the fasting blood sugar in sexually mature females reaches its lowest level in the intermenstruum, rises gradually with the beginning of the premenstruum, gains its maximum on the first day of bleeding, and then returns to the intermenstrual level at the end of menstruation. Similar findings have also been reported by Pucher and others[14] on this continent. A number of Italian workers[15, 16, 17] also studied this problem. They all agree that at menstruation there occurs a rise in the blood sugar, some claiming that in spite of this the blood sugar remains within normal limits and others claiming that an actual hyperglycæmia results. Garafi and Ruggeri performed as many as 1,000 glucose tolerance tests on 93 healthy females at different parts of the menstrual cycle. Their lowest blood sugar values were found at about the time of ovulation; a rise occurred during the premenstruum and reached its maximum with the onset of menstruation. Then the values gradually dropped again to reach a minimum level within 12 days.

The influence of menstruation on the course of diabetes was investigated by the two following methods: (*a*) A statistical review of cases of diabetic acidosis in females who were menstruating regularly, to observe the incidence of acidosis at the time of menstruation. (*b*) An investigation of blood sugars before, during, and after menstruation.

Review of Cases of Diabetic Acidosis

An examination was carried out of the hospital records of all female diabetics between the ages of 14 and 45 years who were admitted in acidosis to the Royal Victoria Hospital from 1922 (date of beginning of insulin therapy) to 1940. This age-group covers the period of sexual activity and extends from puberty to the menopause. The records were searched as to whether the patient was menstruating at the time of admission to the hospital. The case history occasionally indicated when the patient's last menstrual period had occurred, and a few instances yielded the information that the patient was menstruating when the symptoms of acidosis were developing, even though she was not menstruating at the time of entrance into the hospital. These sources of information are naturally imperfect. The error however, is more likely to be one of failing to record menstruation when this was occurring.

Our purpose was to observe what percentage of the cases menstruated on admission to the hospital or just before or after. Those cases were therefore omitted whose records indicated that they were amenorrhœic, or where puberty had not yet occurred. Furthermore, since the

aim of the investigation was to observe if menstruation could disturb a case of presumably controlled diabetes, those cases were also omitted that had entered the hospital for the first time and had not had any previous diabetic treatment, as well as those cases that were complicated by infection. The latter had temperatures ranging from 100° F. to 105.8° F., and infections alone are known to upset cases of well-controlled diabetes.

TABLE I.

ANALYSIS OF CASES OF FEMALE DIABETICS, AGE 14 TO 45 YEARS, ADMITTED IN ACIDOSIS FROM 1922 TO 1940

Type of cases	*No. of cases*
Cases before puberty	7
Cases with amenorrhœa	5
Cases with infection	5
Cases admitted to hospital for first time. (Not treated before)	17
Treated cases, without infection, not menstruating on admission	19
Treated cases, without infection, menstruating on admission	17
Total	70

RESULTS

Table I shows an analysis of all the cases. Of a total of 70 female patients in diabetic acidosis between the ages of 14 and 45 years there were 36 who were menstruating regularly, who had been treated for diabetes previously, and who did not manifest any infection on admission to the hospital. Of these 36 cases 17 were menstruating on admission or two days before or after admission. That is, in 47.2 per cent of the cases of acidosis in which the precipitating cause was neither infection nor lack of treatment, menstruation occurred at or about the time that the acidosis developed. These figures indicate the number of hospital admissions. The number of patients in this series of admissions was smaller. The 36 admissions were composed of only 14 patients and of this number 6, or 42.8 per cent, were admitted in acidosis at the menstrual period or just before or after on one or more occasions. There were also some cases who were admitted in acidosis during the menstrual period at one time and who at another time developed acidosis during the interval between two periods.

In looking through our series of cases of diabetic acidosis one was also impressed by the small number of males as compared with females. Therefore a search was made of the number of male cases of acidosis between the ages of 14 and 45 years irrespective of the cause. This number consisted of only 26 admissions as compared with 70 female admissions in the same age period. That is, of a group of 96 cases of acidosis in patients of ages 14 to 45 years, 27 per cent were males and 73 per cent were females. The difference becomes noteworthy when one realizes that in this age-period the incidence of diabetes is greater in the male than in the female.[1]

BLOOD SUGAR INVESTIGATION AT MENSTRUAL PERIOD

In a series of eleven menstruating diabetic females the blood sugar was determined before, during, and in some cases after the menstrual periods. During the time of investigation each patient was following a constant diet and taking a constant dose of insulin. Eight of these were Out-Door clinic patients. In these the blood sugar was examined on every occasion at about 2½ hours after breakfast. The blood sugar was generally estimated every second day before, during, and, in some cases, after the menstrual period. The remaining three were ward patients. In two of these the blood sugar was examined under fasting conditions and at four hours after the morning insulin, while in the third case (F.D.) it was examined at these periods as well as at 1½ hours after lunch and at 9 p.m. In the latter case as well as in one of the other two ward cases, the CO_2 combining power was determined at the same time. The blood sugars were estimated by the Folin-Wu method and the CO_2 combining power by the volumetric Van Slyke technique.

RESULTS

The findings, on the whole, did not substantiate the results obtained in the first part of the investigation. Most of the patients failed to show any noteworthy disturbance of the carbohydrate metabolism at the menstrual period. Quite a number did manifest some rise of the blood sugar values during menstruation, but this rise was generally small. In comparing the mean sugar values (Table II) during menstruation with those before and after it was found that 2 of the 11 cases showed a lower mean during menstruation, while the remaining 9 showed a higher mean value during the period. In these 9 cases the difference between the menstrual and premenstrual blood sugar values varied between 8 and 115 mgm. per cent, while that between the menstrual and postmenstrual values varied between 3 and 170 mgm. per cent.

TABLE II.

COMPARISON BETWEEN MEAN BLOOD SUGAR VALUES BEFORE, DURING AND AFTER MENSTRUATION

Case	*Blood sugar—mgm. per cent* Premenstrual	Menstrual	Postmenstrual
A.N. 2½ hours after breakfast	108	101	...
B.L. " " " "	137	118	...
G.N. " " " "	114	132	...
M.W. " " " "	187	202	176
C.D. " " " "	208	312	260
D.L. " " " "	172	209	172
R.B. " " " "	...	370	150
M.N. " " " "	107	165	128
E.D. (*a*) fasting	93	132	117
(*b*) 4 hours after morning insulin	96	104	101
A.L. (*a*) fasting	314	324	220
(*b*) 4 hours after morning insulin	188	231	186
F.D. (*a*) fasting	399	440	344
(*b*) 4 hours after morning insulin	241	356	242
(*c*) 1½ hours after lunch	374	401	335
(*d*) 9 p.m.	218	143	162

It should be noted here that in a few cases the blood sugar rise began to appear just before menstruation and, as in case F.D. (Fig. 1), may have reached its peak immediately before the onset of menstrual bleeding. The most striking findings were in Case F.D. (Fig. 1), who was admitted to the ward purposely for this investigation and who was studied quite thoroughly. This patient manifested a marked rise of the blood sugar four days premenstrually. This

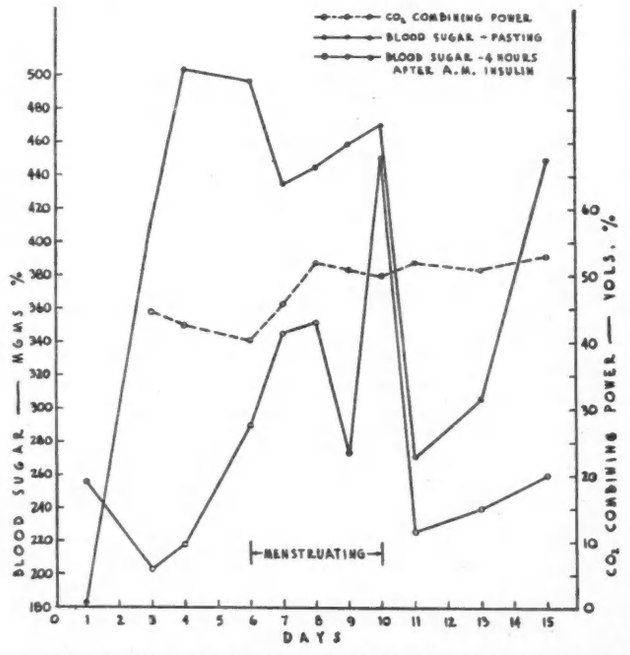
CO₂ COMBINING POWER
BLOOD SUGAR - FASTING
BLOOD SUGAR - 4 HOURS AFTER A.M. INSULIN
BLOOD SUGAR — MGMS. %
CO₂ COMBINING POWER — VOLS. %
MENSTRUATING
DAYS

Fig. 1.—Case F.D., juvenile diabetic. Diet: 70 gm. protein, 50 gm. fat, and 200 gm. carbohydrate. Taking 24 units crystalline zinc insulin before breakfast and before supper. CO_2 combining power was not estimated before the third day after admission. Daily urinalysis showed acetone for first time only on third day.

rise persisted during the period. The drop postmenstrually, however, was comparatively slow and never reached the initial level. The CO_2 combining power was also studied in this case. Four days prior to menstruation it was 44.5 vols. per cent, dropping to 40 vols. per cent one day premenstrually. It rose again, reaching 52 vols. per cent on the second day of menstruation, and remained normal thereafter. During this entire investigation both diet and insulin remained constant. Unfortunately, the CO_2 combining power was not estimated prior to the fourth day premenstrually but acetone and diacetic acid were found in the urine for the first time on that day. The CO_2 combining power was also studied in Case A.L., in whom it remained normal. This patient did not exhibit a pronounced rise of blood sugar values.

DISCUSSION

The results obtained in the first part of our investigation were striking. After excluding the cases of diabetic acidosis associated with the two most common causes of this condition, namely, infection and non-treatment of the diabetes, we were left with a group of 36 cases of which 17, or 47.2 per cent, were menstruating at about the time the acidosis developed. Such a high incidence of the association between menstruation and acidosis cannot be regarded as a mere coincidence. Furthermore, since infection and lack of treatment of the diabetes are not causes of the disturbed carbohydrate metabolism in this series it appears likely that menstruation was the precipitating cause of the acidosis in this group.

It should be noted here that among the 17 cases of acidosis not included in the group of 36, because the diabetes was not treated before admission to the hospital, two were menstruating at the time of admission. Indeed, in one case the history suggested very strongly that the diabetic state started at the menstrual period.

The results of the second part of the investigation are not so convincing. However, most of the patients did show some rise of the blood sugar values at the menstrual period, and in a few this rise was quite marked. In one patient the CO_2 combining power fell to 40 vols. per cent. This was a case of juvenile diabetes which was admitted to the ward merely for investigation and had no complaints whatever. The diabetes appeared to be fairly well controlled before admission. Furthermore, no change in diet or insulin was instituted after admission to

the hospital. On the whole, therefore, the findings in this group of cases do confirm in some degree the conclusions drawn from the first part of the investigation that there is a lowering of carbohydrate tolerance at menstruation. The failure to obtain more striking results may be interpreted as meaning that not all diabetic females show a disturbance of carbohydrate tolerance during menstruation, and that in some cases there may occur such a disturbance at one menstrual period and not at another. This latter phenomenon was illustrated in our statistical study.

E. H. Mason[19] has also observed the case of a middle-aged female whose menstrual periods were frequently delayed by 8 to 12 days. Whenever this delay occurred, the insulin requirement rose from 8 units regular insulin twice daily to 32 units twice daily. When menstrual bleeding set in the insulin requirement gradually returned to its previous level. During the period the diet remained constant. If, on the other hand, the period occurred normally the insulin requirement remained unchanged.

The difference in the incidence of diabetic acidosis in males and females is also striking. There were practically three times as many cases of acidosis in females as in males in the age period in which the normal woman menstruates. This is particularly remarkable when one remembers that the incidence of diabetes is greater in the male than in the female before the age of 45 years.[1] In view of the frequency of diabetic acidosis at menstruation one wonders if the greater incidence of acidosis in young women is not at least partly due to the disturbance in carbohydrate tolerance that occurs in some diabetic females at the menstrual period.

SUMMARY AND CONCLUSIONS

There occurs in some diabetics an impairment of carbohydrate tolerance at the menstrual period. This may be severe enough to precipitate diabetic acidosis and coma. This disturbance in carbohydrate metabolism at menstruation does not occur in all diabetic women. Furthermore, in the same patient this upset may take place at one menstrual period and not at another.

There is also a much smaller incidence of diabetic acidosis in males than in females below the age of 45 years, although in this period the incidence of diabetes mellitus is greater in the male than in the female. This higher incidence of acidosis in the female may be associated with the frequent occurrence of acidosis at the menstrual period.

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PRECEPTS OF EPICTETUS

"Difficulties are the things that show what men are."

"A soul conversant with virtue resembles a perpetual fountain; for it is clear, and gentle, and potable, and sweet, and communicative, and rich, and harmless, and innocent."

"Nothing is meaner than the love of pleasure, the love of gain, and insolence. Nothing is nobler than magnanimity, meekness, and good-nature."

"In every affair consider what precedes and follows, and then undertake it."

"Consider carefully, know thyself, consult the divinity, attempt nothing without God."

THE RELATIONSHIP OF DEGENERATION OF THE THYROID TO PREMATURE AGEING

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THE association of premature ageing with degenerative changes in the thyroid gland first came to our attention with the observations of J. K. McGregor[1] in 1940. The essential observation of this paper was the "premature ageing of patients who are the subject of cystic degeneration of the thyroid, especially when the cyst replaces existing fetal adenoma". At this time Dr. McGregor suggested that some experimental confirmation might be sought, and it was for this purpose that the following experiments were undertaken.

This association of the thyroid with ageing is not new. The symptoms of a patient suffering from nodular toxic goitre have long confused most clinicians. The histopathological explanations of Hertzler[2] in differentiating toxic and degenerative effects have done much to clear this confusion. Hertzler has also championed the relation of bodily ageing and thyroid degeneration, and states emphatically that "man is as old as his thyroid".

As the formation of cysts, whether from fetal adenomata or not, is essentially a degenerative change, we see that these two authors are in accord.

In carrying out experiments, the fluids used were those taken from thyroid cysts at operation. Any type of fluid was used. If the cystic material was hæmorrhagic, it was centrifuged to remove the blood cells and the supernatant fluid was used, as well as a saline suspension of the residue.

The experimental animals were mature white mice, about 8 weeks old. These were kept under standard conditions and the fluids were administered by intraperitoneal injections. At the end of a 6 weeks' period, the surviving mice were killed. In addition to clinical observations of weight, physical activity, sex activity and hair changes; complete autopsies were carried out on all mice used.

Before proceeding to the experiments, there are these observations of importance to be borne in mind: (1) the thyroid in white mice is a very small organ and difficult to prepare for histological section. Macroscopic changes are possible to see, but microscopic ones could not be obtained; (2) the thymus in the normal, adult mouse is a large organ, composed of two lobes and covering most of the anterior mediastinum; (3) ageing mice show sparse and brittle coats.

Experiment 1

Eleven mice were used and observations extended over a period of 55 days. The experimental fluid was obtained from a large, degenerating cyst in a nodular, non-toxic goitre. The fluid was hæmorrhagic in character and was centrifuged. The supernatant fluid was used for injections, as was a suspension of the residue in normal saline. Another group of animals were injected with a suspension of thyroid in distilled water (1 grain, P.D. preparation—100 c.c. and 2 grains—100 c.c.). A final group were kept under similar physical conditions but were not treated in any way.

1. A group of 3 mice were injected with 0.6 c.c. of the supernatant fluid from centrifuged thyroid material. These died within 6 hours. At autopsy, these all showed signs of an acute irritative peritonitis and general toxæmia.

2. One of the mice was again injected with the supernatant fluid from the thyroid cystic material. The dosage was started at 0.1 c.c. and increased over a period of 40 days to 1.0 c.c. The animal was pregnant at the start of the experiment and normal delivery took place. There were no further pregnancies. With injections, there was a steady loss of physical activity. The mouse died on the 40th day. The findings were: (*a*) hair coarse and sparse; (*b*) absence of thymus; (*c*) evidence of generalized toxæmia.

3. Two mice were injected with the saline suspension of the residue from the centrifuged thyroid fluid. The dose was slowly increased from 0.6 to 1.0 c.c. One mouse received injections for 22 days when it suddenly became very ill and died in a few days of a severe, extensive, necrosing peritoneal infection. During injections its hair became sparse and brittle. At autopsy the infection was so widespread that

no definite conclusions could be made. The second mouse received 15 treatments, when it suddenly died. During the experiment it showed a slight but steady weight loss, but maintained its activity. At autopsy, the striking findings were: (*a*) absence of thymus; (*b*) evidence of general toxæmia.

4. Two animals were kept as controls. These showed no variation in weight or hair growth. They were finally killed and at autopsy showed no signs of disease of any kind.

5. Three animals were injected with a suspension of P.D. thyroid, the dosage increasing from 0.6 c.c. of a solution of 1 grain/100 c.c. H_2O to 1.0 c.c. of a solution of 2 grains/100 c.c. H_2O. These animals were all healthy and extremely active. They all tended to gain weight during the course of the experiment. At its termination they were killed and autopsy showed no evidence of disease or glandular change.

SUMMARY—EXPERIMENT 1

Mouse	*Treatment*	*Activity variation*	*Cause of death*	*Post-mortem findings*			
				Hair changes	*Thyroid*	*Thymus*	*Other organs*
10	Supernatant cystic thyroid fluid	No	Acute peritonitis	No	Normal	Normal	Normal
11	Supernatant cystic thyroid fluid	No	Acute peritonitis	No	Normal	Normal	Normal
4	Supernatant cystic thyroid fluid	No	Acute peritonitis	No	Normal	Normal	Normal
9	Supernatant cystic thyroid fluid	Loss	Chronic peritonitis	Sparse and brittle	Normal	Absent	General toxic
2	Saline suspension of residue from cyst	Loss	Chronic peritonitis	Sparse and brittle	Normal	Absent	General toxic
6	Saline suspension of residue from cyst	Loss	Chronic peritonitis	No	Normal	Absent	General toxic
3	None	No	Ether	No	Normal	Normal	Normal
11	None	No	Ether	No	Normal	Normal	Normal
5	Saline suspension thyroid	No	Ether	No	Normal	Normal	Normal
7	Saline suspension thyroid	No	Ether	No	Normal	Normal	Normal
8	Saline suspension thyroid	No	Ether	No	Normal	Normal	Normal

EXPERIMENT 2

This experiment was undertaken under the same conditions as the first. The solutions were: (1) a suspension of 3 grains of P.D. extract/100 c.c. H_2O; (2) supernatant fluid from thyroid cyst used in Experiment 1; (3) about 5 c.c. fluid from an histologically-proved fetal adenoma of the thyroid gland.

Following the results of the first experiment, the purposes sought here were: (1) to note the results of a definite unprogressive dosage rather than a progressive one; (2) to confirm the results obtained in the first experiment; (3) to note the body response to variations in diet under the different types of treatment. The results were as follows.

1. Two animals were used as controls, kept under the same dietary conditions, but otherwise untreated. They showed no hair changes or sharp variations in activity. In response to a very low diet, they lost weight up to 10 to 15 per cent, but rapidly regained it on being placed on a full diet again. Both were killed with ether and autopsy showed no organic change; thyroid normal in appearance and thymus well developed.

2. Four mice were treated with daily intraperitoneal injections of 0.5 c.c. solution, 3 grains P.D. thyroid/100 c.c. water. Of these: one developed an infection of the right orbital region on the 16th day of treatment. This very indolent infection spread slowly, to kill the animal on the 36th day of treatment. Autopsy at this time showed no abnormalities of the viscera of the thorax or abdomen. The thyroid and thymus were quite usual in appearance.

Two of the animals ran the full course of the experiment for 56 days, and showed no outward effect from treatment. Both were killed with ether and autopsy showed the thyroid, thymus and all other viscera to be quite normal. In response to low dietary intake, these animals would lose 10 to 15 per cent of weight in 2 to 3 days and regain it rapidly on return to normal intake.

The fourth mouse developed a severe spreading dermatitis on the 10th day of treatment, became comatose on the 14th and died on the 16th. The nature of the infection was not determined; none of the other animals contracted it. Autopsy showed the thyroid, thymus and other viscera to be normal.

3. The supernatant fluid from a nodular, nontoxic goitre cyst was used in 3 mice. The fluid was injected intraperitoneally, starting at a dosage of 0.3 c.c. and increasing to 0.5 c.c. when it was stabilized. The injections were continuous over a period of 41 days when the experiment was temporarily arrested. On the 50th day, 0.5 c.c. of fluid was injected into each of the animals. All animals died within 4 hours of this last injection. They became drowsy and feverish and rapidly lapsed into coma to be quickly followed by death. During the course of the experiment animals gained and lost weight rapidly in response to dietary changes, showing no difference from the others. Autopsy in these 3 mice showed: (*a*) severe abdominal distension; (*b*) cloudy swelling of liver, kidneys and heart; (*c*) normal thyroid (macroscopic); (*d*) thymus could not be found. Whether these animals died of anaphylactic shock or severe, acute toxæmia is impossible to state. It is interesting to note that the symptoms are suggestive of "thyroid storm".

4. One mouse was given 15 intraperitoneal injections of fluid removed from a fetal adenoma of the thyroid. On the 15th day, the animal was destroyed by other animals. The thorax was rescued, and showed no evidence of thymic remains.

SUMMARY—EXPERIMENT 2

Mouse	*Treatment*	*Activity variation*	*Cause of death*	*Post-mortem findings*			
				Hair changes	*Thyroid*	*Thymus*	*Other organs*
1	None	None	Ether	No	Normal	Normal	Normal
5	None	None	Ether	No	Normal	Normal	Normal
2	Suspension of thyroid	No	Facial infection	No	Normal	Normal	Toxic
4	Suspension of thyroid	No	Ether	No	Normal	Normal	Normal
6	Suspension of thyroid	No	Toxæmia	No	Normal	Normal	Toxic
8	Suspension of thyroid	No	Ether	No	Normal	Normal	Normal
3	Supernatant cystic thyroid fluid	No	Anaphylaxis (?)	Sparse and brittle	Normal	Absent	Normal
7	Supernatant cystic thyroid fluid	No	Anaphylaxis (?)	Sparse and brittle	Normal	Absent	Normal
10	Supernatant cystic thyroid fluid	No	Anaphylaxis (?)	No	Normal	Absent	Normal
11	Fluid from fetal adenoma	No	Killed	No	Normal	Absent	.....

EXPERIMENT 3

These last observations, conducted under the same standards as before, were conducted partly to confirm, again, the results previously obtained, using now thyroid cystic material obtained from another patient suffering from nodular toxic goitre. The fluid on this occasion was not hæmorrhagic and was not centrifuged. In an attempt to demonstrate that the effects obtained were not due to any cystic fluid, one set of animals were treated with fluid removed from a large, benign, ovarian cyst. (Patient aged 37). The results were as follows.

1. Control animals from the same litter lived an entirely healthy life and at autopsy showed no organic disease.

2. Four mice were injected daily with fluid from the ovarian cyst, the standard dose being 0.5 c.c. Experiments were carried out over a period of 34 days. These mice were entirely

healthy throughout the experiment. At autopsy, no organic disease was present and the thyroid and thymus were normal in development.

3. The three remaining mice were treated with daily injections of 0.5 c.c. of thyroid cystic material over a period of 34 days. These animals led a healthy life, but 2 of the 3 showed thinning and coarsening of the hair. At autopsy, all three of these seemed normal except for a complete disappearance of the thymus gland.

SUMMARY OF EXPERIMENTAL FINDINGS

1. Fluid obtained from thyroid cysts (degenerative or fetal) is extremely toxic to mice in large doses (0.6 c.c.), causing death in a few hours, but can be injected in smaller doses with safety. However, animals so treated become sensitized to the material and injection, after a period of rest, causes rapid death by what appears to be an anaphylactic reaction.

2. Intraperitoneal injection of all different types of thyroid cystic material, causing complete thymic atrophy in all mice so treated. That this was not due to infection, is evident in that animals treated otherwise and dying of infection showed no thymic changes. That it was not a reaction to human blood or body proteins is likewise evident; in that one given the thyroid cystic material was free from blood; one group of animals treated with ovarian cystic material showed no pathological changes whatsoever.

3. Sixty-five per cent of animals treated with cystic thyroid material showed hair changes, the fur becoming sparse and coarse. This is a recognized sign of age in these animals. None of the other animals showed these changes.

4. Mice so treated did not lose weight, but did lose sexual activity.

5. Mice treated by intraperitoneal injection of suspensions of thyroid extract in distilled water showed no evidence of organic changes.

6. Control mice of the same litter showed no symptoms of ageing at the end of the experiments, either clinically or pathologically.

DISCUSSION

In several respects, the above experiments are not complete. Thus we would have liked to carry out observations on testes and ovaries, but were unable to do so. Clinically, observations as to sexual activity were most unsatisfactory, due to lack of facilities.

Bearing in mind Hertzler's observations on the cardio-toxic goitre, microscopic studies on the heart and large vessels were carried out, but were repeatedly negative. Again, accurate observations of intelligence were not possible, due to lack of facilities; attempts were made, but were so unsatisfactory as to be omitted. However, from the experiments, two facts of importance emerge.

In the first place, two-thirds of the animals showed changes of the hair and skin, which are usually associated with ageing of mice. These observations were confirmed in all three studies.

The second fact is that all animals treated by intraperitoneal injection of cystic thyroid material showed total thymic involution. The physiology of the thymus gland is such a dark field that interpretation of such findings is difficult. Anatomists are agreed, however, that after puberty the thymus involutes quickly, to be almost non-existent in the final decades. And

SUMMARY—EXPERIMENT 3

Mouse	*Treatment*	*Activity variation*	*Cause of death*	*Post-mortem findings*			
				Hair changes	*Thyroid*	*Thymus*	*Other organs*
1	No	No	Ether	No	Normal	Normal	Normal
2	No	No	Ether	No	Normal	Normal	Normal
3	Fluid from ovarian cyst	No	Ether	No	Normal	Normal	Normal
4	Fluid from ovarian cyst	No	Ether	No	Normal	Normal	Normal
5	Fluid from ovarian cyst	No	Ether	No	Normal	Normal	Normal
6	Fluid from ovarian cyst	No	Ether	No	Normal	Normal	Normal
7	Thyroid cystic material	No	Ether	Sparse and brittle	Normal	Absent	Normal
8	Thyroid cystic material	No	Ether	Sparse and brittle	Normal	Absent	Normal
9	Thyroid cystic material	No	Ether	No	Normal	Absent	Normal

so it would seem that a mouse, whose thymus has been completely involuted, must be an aged one, even though that ageing be prematurely produced by artificial means.

So much for the original purpose of these experiments, which are sufficiently confirmed by the above findings. But they have brought up another point which may prove of great interest. Most previous thought on the inter-relationship of thyroid and thymus, has been based upon the work of Hammar. He established that true exophthalmic goitre was accompanied by marked thymic hypertrophy, and his observations are quoted by thyroid surgeons, pædiatricians and others interested in such studies.

The above experiments, however, have shown that the degenerative products of nodular goitres, whether toxic or non-toxic, will produce involution of the thymus gland. This is a field not yet investigated or reported on. However, the implication is that here we have a totally different disease, producing opposite effects in relation to the thymus and presumably in relation to the rest of the body. We may presume, perhaps, that such hyperplastic effects as are noted are due to secretions from abnormal attempts at regeneration, which we know to exist. And so we may say that in such patients, the evidence of hyperplastic symptoms is of little importance as compared to ageing, cardiac complaints, or even the presence of an enlarged thyroid gland.

This conception of thyroid disease with primary degenerative effects and secondary toxic effects is one which merits further consideration and study.

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CHOLESTEROL AND THE HEART: ITS EFFECT ON THE ACTIVITY OF THE HEART OF THE FROG AND THE TURTLE*

BY JOHN FERGUSON

Edmonton

THE physiological effects of cholesterol have a practical as well as a theoretical interest. Horrall[1] in his very readable book, "Bile: Its Toxicity and Relation to Disease", has outlined much of the reported work bearing on the physiology of cholesterol. A real difficulty has been to find a suitable menstruum in which to disperse cholesterol in a satisfactory form for injection. In many instances the solvent used could have a profound influence. In 1907 Danilewsky[2] reported that he applied cholesterol in Ringer's in concentrations of 0.001 to 0.003 per cent directly to the heart of the frog. He concluded that cholesterol increased the force of the beat. The increase was noticeable in 20 to 30 seconds and reached a maximum in 2 to 4 minutes. Then the beat decreased below the normal contraction. Lecithin, he intimated, had an even greater stimulating action on the heart.

There is no way of ascertaining the purity of the cholesterol used in many of the reports published at the beginning of the century. However, the melting-point of cholesterol in 1906 is given as 145° C.[3] while at the present time it is considered as being 148.5° C.[4] The optical activity of cholesterol as recorded in 1913 and 1927 is indicated as variable.[5, 6, 7] Moreover, hyper- or hypocholesterolæmia is not usually associated with variations in the heart-beat. Accordingly, it was decided to ascertain the effect, if any, of the highly purified product obtainable today on the activity of the heart of the frog and the turtle.

METHODS

Ringer's solution for amphibia (0.6 per cent NaCl; 0.03 per cent KCl; 0.026 per cent $CaCl_2$ in distilled water) was placed in a hard glass flask. To this was added chemically pure cholesterol ($C_{27}H_{45}OH$) in excess. The mixture was heated from 50 to 60° C. and kept at room temperature for several days to assure saturation. Plain Ringer's solution was kept in a similar flask to assure uniformity of conditions. Cholesterol is stated to be soluble in distilled water to the extent of 0.26 grams per 100 millilitres at 20° C.[4]

The frog was prepared in the ordinary way for recording the heart-beat and a record made on a lightly smoked drum. The level was a light straw and the mechanical advantage about 1:12. In all twelve frogs were used. The majority of records were of forty minutes' duration approximately. The turtle was prepared largely as outlined by Laurens[8] and the atrium and ventricle suspended so as to record their movements on a drum. Alignment marks were made intermittently on the

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tracing for convenience in determining the conduction time. Measurements for the A-V interval were made at the most convenient alignment marks with a vernier caliper and reading glass. Records were of approximately two hours' duration. In all five turtles were used. As this work was carried on during April and May the mean diurnal room temperature near noonday was about 30° C.

In each instance care was exercised to keep conditions uniform throughout the experiment as regards such factors as application of solution, temperature, etc. Ringer's solution was applied continuously to the heart for a period, then Ringer's saturated with cholesterol, and finally powdered cholesterol was sprinkled on the heart followed by Ringer's solution. The powdered form was applied to obtain the greatest concentration of cholesterol possible.

RESULTS

At least 12 determinations of both rate and amplitude were made in the case of each frog. The rate and amplitude of the recorded beat were determined before and after the application of cholesterol. The following are the averages obtained. Immediately before cholesterol 48 beats per minute, 27.8 mm. amplitude; immediately after cholesterol 49 beats per minute, 27.8 mm. amplitude; three minutes after cholesterol 48 beats per minute, 29.4 mm. amplitude; ten minutes after cholesterol 47 beats per minute, 27.5 mm. amplitude. The averages of the greatest amplitude before and after cholesterol were 29.1 millimetres (48 per minute) and 31.0 millimetres (49 per minute). In 6 to 12 minutes after cholesterol had been added three hearts manifested apparently delayed conduction. After a prolonged period irregularities were observed, also. The rate, amplitude of the ventricle and A-V interval were determined in each of five turtles. From 14 to 29 determinations were made in each case before, after the addition of cholesterol dissolved in Ringer's, and after powdered cholesterol. An average for each period was determined for each turtle and then an average was made for the five turtles. The following results were obtained. Normal with Ringer's: rate 49 per minute, amplitude 15.5 mm., A-V interval 0.63 second. After cholesterol in Ringer's: rate 51 per minute, amplitude 16.1 mm., A-V interval 0.67 second. After Ringer's and powdered cholesterol: rate 44 per minute, amplitude 14.7 mm., A-V interval 0.69 second.

It was deemed advisable to make further determinations and to average the results at stated intervals, as it has been suggested that cholesterol led to an increase in cardiac activity then to a decrease. The following results were obtained. Normal, 3 minutes before cholesterol: rate 49 per minute, amplitude 14 mm., A-V interval 0.62 second. Normal, immediately before cholesterol: rate 49 per minute, amplitude 14 mm., A-V interval 0.69 second. Cholesterol, immediately after: rate 48 per minute, amplitude 15 mm., A-V interval 0.67 second. Cholesterol, 5 minutes after: rate 49 per minute, amplitude 15 mm., A-V interval 0.60 second. Cholesterol, 11 minutes after: rate 51 per minute, amplitude 16 mm., A-V interval 0.63 second. Cholesterol, 17 minutes after: rate 51 per minute, amplitude 15 minutes, A-V interval 0.63 second.

When tracings were made over a period of approximately three hours it was observed that the amplitude was well sustained but that the A-V interval lengthened. At 135 minutes after the addition of cholesterol it was found in the case of 3 turtles that the average amplitude was 14 mm. and the average A-V interval was 0.93 second. Irregularities in the beat were also observed after a prolonged period of cholesterol application.

DISCUSSION

Professors Best and Taylor[9] in their excellent book remark "that there is a great deal to be learned concerning the physiological significance of the sterols". Many would probably concur in this opinion. Degkwitz[10] ably marshalled a good deal of evidence to show that cholesterol antagonizes lecithin. Seel[11] advanced the interesting theory that cholesterol is a sort of "physiological digitalis". Bodansky and Bodansky[12] have mentioned a few of the pertinent reports in respect to cholesterol and the heart. When considering the relation of cholesterol to abnormal cardiac conditions the suggestion is sometimes made that, as the amount of cholesterol in the blood varies at different periods of life, this variation and supposedly resultant effect are merely concurrent changes. However, Page *et al.*[13] have found that the cholesterol of the blood plasma of normal men varied little at different periods of life.

In this work it was found that the heart of the frog and the turtle exhibited a slightly increased contraction after the application of cholesterol. After prolonged application conduction time showed evidence of being increased. This last observation is of interest, as Cashin and Moravek[14] prepared cholesterol and injected it intravenously into a cat. The electrocardiogram showed "marked prolongation of the P-R

interval, inversion of the T wave, extra systoles occurring in bigeminæ, also short paroxysms of ventricular tachycardia and, in some cases, complete heart block."

SUMMARY

1. After the application of cholesterol to the heart of the frog and the turtle the amplitude of the beat showed a slight increase.

2. Irregularities appeared in the beat after the prolonged application of cholesterol.

3. In the case of the turtle where the application of cholesterol was continued for 135 minutes the conduction time was lengthened approximately 50 per cent.

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Case Report

THE TORKILDSEN PROCEDURE FOR INOPERABLE OCCLUSION OF THE SYLVIAN AQUEDUCT*

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In 1939, Dr. Arne Torkildsen, of Oslo, described a new operation designed to relieve the obstructive hydrocephalus caused by occlusion of the aqueduct of Sylvius.[1] The author's studies of the ventricular system during the four years which he spent in Montreal are well known. The procedure which he has now described is a useful contribution to the care of a distressing and usually incurable group of cases. It provides relief of headache with a minimum of disturbance and gives time for adequate radiation of infiltrating tumours where this is indicated.

Torkildsen reported the use of this procedure in three cases, in all of which there was a considerable amount of dilatation of the lateral ventricles, symptoms of increased intracranial pressure, and evidence of a neoplasm in the vicinity of the aqueduct of Sylvius. In two of his cases the neoplasm only caused occlusion of the aqueduct; in the third case there was evidence of an infiltrating tumour in the region of the basal ganglia and the thalamus.

The procedure is as follows. A rubber catheter is passed through a trephine hole in the occipital region into the lateral ventricle. The catheter is brought out, passed underneath the scalp, but outside the dura, into the suboccipital region. Here a small suboccipital decompression is done to enlarge the exposure of the dura over the cisterna magna. The end of the catheter is then sutured to the soft tissue at the foramen magnum, and its free end allowed to open into the cisterna magna. Torkildsen cut out a groove in the skull and underneath the scalp wide enough to allow the catheter to remain in a sort of a trough.

CASE REPORT

This patient was a young woman, aged 27, who seven months previous to admission began to have headaches which were at times associated with vomiting. For two months the headaches had become quite severe and were principally situated in the right occipital region. About six months before admission she noted decrease in her vision, and, for about three weeks, loss of hearing in both ears and more rapid failure of vision. Meanwhile, the headaches had become very acute. She complained also of buzzing in both ears, which had been present about two weeks, and recent attacks of numbness in the left arm and face.

On examination the patient was found to be alert and complaining particularly of headache. The hearing loss seemed to increase during the time she was in the hospital. She had a bilateral papillœdema; there was impairment of visual acuity; the right pupil was slightly larger than the left; both reacted to light; there was no nystagmus; the deep reflexes were not increased and were about equally active on the two sides; plantar responses, flexor; abdominal reflexes, present, although the left abdominal reflex was less active than the right. Simple x-rays showed rarefaction of the sella turcica, suggestive of an expanding intracranial lesion.

* Report of a case presented at a meeting of the Montreal Neurological Society, April 15, 1942.

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Trephine holes were made in the occipital region on both sides and a ventriculogram carried out. This showed that the lateral ventricles were much enlarged as well as the anterior part of the third ventricle. The third ventricle just posterior to the massa intermedia was obliterated. Oxygen would not enter this region when the brow was down and there was no visualization of the aqueduct of Sylvius or the fourth ventricle or basal cistern. The conclusion of Dr. Arthur Childe after studying the ventriculograms was as follows "There is an expanding lesion situated in the posterior portion of the third ventricle. The slight elevation in the floor of the lateral ventricle on the right side suggests that there may also be some involvement of the right optic thalamus".

Our general conclusion was therefore that this patient had a tumour which was almost certainly infiltrating in the region of the thalamus of the right side and quite possibly extending into the region of the medial geniculate body.

It was decided to carry out the procedure of Torkildsen, and, if this should relieve the pressure, to give the patient deep x-ray therapy.

Torkildsen's procedure.—The scalp incision which had been used for the trephine hole was reopened and enlarged very slightly. A ventricular needle was passed into the ventricle and withdrawn. A catheter, No. 12, was then inserted into the ventricle. A groove was cut in the bone with a rongeur, tunnelling for a little distance underneath the unopened scalp. An incision was then made in the suboccipital region. The catheter was passed down underneath the scalp and allowed to emerge in the new incision. The suboccipital muscles were separated in the midline, and slight enlargement was made of the cisterna magna, cutting a groove in the bone up over the left cerebellum so that the catheter could lie in a bony groove there as well. The dura was opened. The catheter was then cut off to a proper length and introduced through a small opening in the dura and arachnoid just inside the cisterna magna. The dura was sewn around the end of the tube, a silver clip placed on the dura at that point to serve as a localizer in x-rays later, and the tube was sewn to the dura.

With both incisions open, the head was then moved in all directions. It was found that, inasmuch as the catheter hugged the skull closely all the way round, movements of the neck did not cause any shift in its position. It was therefore concluded that a flexible metal catheter could quite well be used for this purpose. It was quite obvious that spinal fluid escaped freely from the ventricle into the cistern. Muscle and skin were closed in layers over the tube. The whole procedure was carried out under local anæsthesia without discomfort. Post-operative x-ray plates showed the catheter to pass into the intracranial cavity about 5 cm. through the occipital opening, and demonstrated the other end of the catheter just beneath the silver clip which was placed upon the margin of the dura over the cisterna magna.

From the time of the operation the patient's headaches disappeared. Deep x-ray therapy was begun at once, and during the period that she remained in hospital her hearing improved greatly.

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Special Article

REPORT ON "GLYOXYLIDE" BY THE ONTARIO COMMISSION FOR INVESTIGATION OF CANCER REMEDIES*

Reference has been made in several interim Reports of the Commission to "Glyoxylide", a substance sponsored by Dr. David H. Arnott, of London, Ontario.

In reporting at this time, it seems desirable to briefly review the matter from the inception.

Dr. Arnott is a physician and surgeon who has been practising medicine for some forty years in London, Ontario. Soon after the constitution of the Commission in 1938, Dr. Arnott, after communicating with the Commission, appeared at a sitting with his counsel, first on November 30, 1938. He had been for some time using a substance called "Glyoxylide" in the treatment of cancer. This was said to have been perfected by, and the formula of it to be the property of, one Dr. William F. Koch, Detroit, Michigan. This substance was claimed to be a remedy or cure for cancer. It was claimed that it had been used widely not only in the United States of America but also in Europe, and by Dr. Arnott in Ontario, with beneficial results.

At the outset, Dr. Arnott stated that since the constitution of this Commission he had discontinued its use, thinking that if he continued he might be required under Section 6 of the Cancer Remedy Act 1938 to submit samples and/or the formula thereof. He submitted that by discontinuing the use of the substance he did not come within the provisions of this section. First he desired to enter into an agreement with the Commission whereby he would co-operate with the Commission "to the end that the Commission will be able to satisfy itself that the Koch treatment has a definite therapeutic value in the treatment of cancer, and in the event of such approval being given by the said Commission" Dr. Arnott would "use his best efforts to have the formula and methods of treatment revealed." The Commission declined to enter into such an agreement, as it would mean its being asked to judge on statements regarding the substance without its experts being allowed to use it, or without having the formula itself.

Subsequently Dr. Arnott communicated with the Commission signifying his willingness to stand as sponsor for the substance to be investigated, and assured the Commission of his co-operation. The Commission desired to have an investigation of the substance, consisting both of clinical and laboratory studies, and to this Dr. Arnott agreed. He desired first to submit to the Commission certain clinical evidence consisting of case histories and the testimony of and concerning certain patients who had been treated with this substance. The Commission indicated it would require to have the substance investigated to its satisfaction both on the clinical and labora-

* As of February 7, 1942.

tory side, but to meet the sponsor's request it was arranged to first hear the evidence which he desired to present. In view of the fact that he practises at London and a number of the case histories which he desired to present, and the patients whom he desired to call as witnesses, were said to be from that locality, a Committee of the Commission met with him in London in 1939 and there took such evidence as he had to offer, for the most part consisting of case histories and the presentation of a number of patients who had been treated by him. In all, the evidence of some eight witnesses was heard before the committee at that time, and this was subsequently reported to the Commission as a whole.

Later, Dr. Arnott attended with his counsel before a sitting of the Commission at Toronto and there presented considerable further evidence, in part consisting of a number of witnesses who had previously testified before the Committee in London.

The cases presented fall into two groups, those treated with Glyoxylide in the United States and those treated in Canada. There were about twenty American cases presented. Of these, seven were submitted by Dr. J. W. Kannel, of Fort Wayne, Indiana, who appeared personally before the Commission. In the Group of American cases there were some in which, according to the reports submitted, the diagnosis of cancer had been well established and in which recovery occurred after treatment with Glyoxylide and nothing else, but the Commission does not believe that a critical review of the American cases presented would be of material value in its attempt to find out whether Glyoxylide has a beneficial effect on Cancer. There are several reasons for this conclusion. (1) The Commission is unable to assess the standing of certain laboratories throughout the United States which have made biopsy and pathological reports on the cases submitted. (2) Dr. Koch has been using his treatment for at least 20 years. It was stated by a nurse in his employ that 3,000 doctors are administering Glyoxylide. It may be inferred therefore that several thousand people with Cancer or alleged Cancer have been treated with Glyoxylide. Out of these thousands no doubt the best cases were presented to the Commission. In any large series of cases diagnosed as cancer, there may be a few mistakes by the best pathologists, surgeons or x-ray specialists, and these mistakes might be responsible for some of the alleged cures. In other words, the diagnosis of Cancer might have been wrong. It is in a group of several thousand cases that a few such errors might creep in. Further, there is the rare case of spontaneous regression or recovery from Cancer to be considered. (3) The valuation of any treatment for a more or less chronic disease like Cancer, where the investigation must be confined to the review of cases treated, is exceedingly difficult. It is important to have a fairly large number of cases for investigation—not a few cases selected from many. What is required is the percentage of recoveries and inferentially the number of failures. This is a fundamental principle which is observed by surgeons and radiologists, by clinics and hospitals. The Commission has not been able to learn how many patients have been treated directly or indirectly by Dr. Koch in the last twenty years nor what percentage have recovered. To put it more plainly, the Commission ought to know how many cases of proved Cancer recovered after treatment by Glyoxylide alone and how many died.

Among the Canadian cases presented, two were not examples of Cancer but of Endarteritis Obliterans. These were introduced to clarify the theory underlying the Glyoxylide treatment. This is briefly that Cancer and many other diseases are the result of "defective physiological oxidation", that the defect is chemical and that Glyoxylide overcomes this defect. It is claimed that this substance may benefit or cure Cancer, Coronary disease, infections like Tuberculosis, Anterior Poliomyelitis and Leprosy, Eczema, Angeioneurotic Œdema, Hay fever, Asthma, Endarteritis Obliterans, Psoriasis, and benign tumours. Its use is therefore urged in all these conditions.

The following brief comments may be made on cases presented as having been treated by Dr. Arnott personally: Case (*a*) patient died of cancer; (*b*) patient died of cancer; (*c*) a case not of cancer but Endarteritis Obliterans. Said to have resulted in recovery; (*d*) there is no diagnosis by biopsy. The history is not characteristic of cancer, but could be more easily explained as an inflammatory lesion. The diagnosis of cancer is, to say the least, questionable; (*e*) diagnosis by clinical methods and x-ray. The x-ray diagnosis was not positive, and the clinical picture and history could be explained by an inflammatory lesion, as for example, Diverticulitis; (*f*) the clinical diagnosis is questionable. On the history it was thought a better diagnosis might be made; (*g*) positive diagnosis of cancer lacking; (h) on the evidence there would undoubtedly be difference of opinion among experts as to the real diagnosis; (*i*) diagnosis of cancer in this case by microscopic sections. Treatment: surgery and "Glyoxylide" and patient gradually recovered and has remained free from symptoms of the old trouble. On somewhat conflicting evidence the question arises as to whether the patient was cured by surgery or by "Glyoxylide"; (*j*) treatment by radiotherapy and "Glyoxylide". There remains the question as to whether the benefit was derived from radiotherapy or "Glyoxylide".

Case histories of five cases were presented on behalf of the sponsor, Dr. H. N. Candlish, of Montreal. One of these was a case, not of cancer but of Endarteritis Obliterans, and of the others, one contained insufficient detail to be of assistance. Two concerned cases where the reports were made at a time when it was too soon to

draw any conclusions, and in the remaining case the diagnosis was speculative.

Four cases were reported by letter from Dr. J. F. B. Rogers, of Port Burwell, Ont., but owing to lack of detail they are not of assistance for the purposes of the Commission.

Considerable weight was attached by Dr. Arnott to a communication said to be from Professor Maisin, formerly in charge of the cancer centre attached to the University of Louvain, Belgium. It is said that Dr. Maisin had used Glyoxylide to some extent in Europe. He was at the time said to be in the United States, and Dr. Arnott was invited to arrange for his attendance before the Commission. It was found that this was not possible; but in letter under date of September 9, 1939, he stated that over a period of five years he had seen cancer disappear in animals and in men as a result of the use of Glyoxylide. He concluded his letter as follows:

"It is of course too early to conclude, but sometimes the results have been so striking that we feel fully justified to continue the research in this field."

Although it is said that Glyoxylide has been used extensively in the United States, inquiry failed to elicit any report made there by any recognized authority of assistance to the Commission. A reliable medical source advised the Commission of two patients who formerly were connected with a nursing home and later a private hospital in Detroit. These patients were familiar with the Koch treatment, and once a year one of them received a prophylactic dose of "Glyoxylide", the last in January, 1941. Both patients are said to be now suffering from cancer.

Dr. Arnott advised the Commission that he lacked current clinical cases to prove the value of the substance, and expressed himself as ready and willing to treat patients under the observation of the Commission or its agent if cases could be found. As a result, through arrangements made by Commissioner Dr. Valin, Dr. Arnott attended in Ottawa and treated ten cases. These cases were carefully observed by Dr. Valin and a qualified medical observer appointed by the Commission, and full reports thereon have been made to and considered by the Commission. In connection with these cases, Dr. Valin and the medical observer in charge reported in part as follows: "out of nine (9) patients with positive biopsies for cancer and treated with Glyoxylide, nine (9) or 100 per cent are dead. The other case who is well did not have cancer."

SUMMARY

Case No.	*Diagnosis*	*Number injections*	*Radiation*	*Days lived after injection*	*Final result*
1	Cancer of skin.....	one	yes	176	dead
2	Cancer of hypopharynx.....	two	no	255	dead
3	Diverticulum of sigmoid.....	one	no	living and well	
4	Cancer of sigmoid...	one	no	262	dead
5	Cancer cervical glands—sec.....	one	yes	151	dead
6	Cancer of rectum...	one	no	334	dead
7	Cancer of bladder...	one	no	29	dead
8	Cancer of pancreas..	one	no	212	dead
9	Cancer of breast....	one	no	226	dead
10	Cancer of œsophagus	one	no	161	dead

"From the standpoint of prolongation of life, regression of tumour, suppression of symptoms in the nine cases of cancer treated by glyoxylide and observed by us until their final termination, we failed to observe any curative or remedial effect of the drug, namely *Glyoxylide*, as administered by Dr. David H. Arnott."

As intimated, it was pointed out to the sponsor early in the proceedings that the Commission desired both clinical and laboratory investigations. The Commission has repeatedly asked for some co-operation in this respect, and although Dr. Arnott has from time to time voiced his desire to co-operate, the Commission has never been able to obtain a sample of the substance in question or to observe or learn its exact method of preparation. Two printed volumes were submitted to the Commission entitled "Natural Immunity, Its Curative Chemistry in Neoplasia — Allergy — Infection", and "The Chemistry of Natural Immunity". These were said to be the work of Dr. Koch with the assistance of Dr. Arnott and were said to contain complete information respecting "Glyoxylide" and particulars of its formula. In the opinion of the Commission, this did not contain satisfactory information.

After much negotiation, the Commission finally, with Dr. Arnott's consent, named Dr. A. B. Macallum, Dean of the Medical School of the University of Western Ontario, to make such investigation on the laboratory side as he might think desirable in connection with the substance. Arrangements to do this were never carried out, due to objections by Dr. Arnott, and the Commission has been unable to get any further co-operation in this respect.

A careful review of all the evidence presented at this date, fails utterly, in the opinion of the Commission, to support the claim made on behalf of the Koch treatment that it is either a remedy or cure for cancer.

Clinical and Laboratory Notes

MEDICAL NOTES FROM WEST AFRICA

LABORATORY REPORT, 1941

BY ALICE K. STRANGWAY

Bie, Angola, West Africa

The laboratory work in Chissamba Hospital grows from year to year. It is proving to be a source of ever increasing pleasure to the worker in charge of it.

During the past year Domingoe, a graduate of Currie Institute, and Massey, a graduate of third year high school in Huambo, have done a great many of the routine examinations. It is best to have workers with the highest training which they can get because more responsibility can be given to them in the laboratory work, than to those with a poorer educational background.

About 4,500 examinations have been done this year in this department, including blood smears for malarial and relapsing fever parasites and anæmias, tissue examinations for cancer, etc., nasal scrapings for the bacillus of leprosy, urinalyses, sputum examinations for the bacillus of tuberculosis, blood tests for syphilis, fæces examinations for the prevalent intestinal parasites, spinal fluids, blood counts, examinations for bilharzia, etc.

Several diseases have been discovered in the laboratory this year which previously we had not known existed in this country. The parasites of kala azar were discovered in the fluid from a liver puncture and two diseases caused by fungus growths were identified by the use of the microscope. Several children have been found to have a species of tapeworm which during our other years we had not found.

Leprosy seems to be on the increase and the bacillus has been found in sixty-seven new cases during the past year. We are happy to be able to record that some of these patients were early cases. When a positive diagnosis can be made in these early cases, there is great hope for a complete cure. Because in native society a stigma is attached to a leper, we find mainly advanced cases appearing for treatment. But we are trying by educational work to encourage them to come when the first spot appears.

The new incubator for bacteriological work which arrived from England in spite of war conditions has been connected to the electric system and has already begun its service as an aid to diagnosis of disease. Three cases of Malta fever and one of pneumococcal meningitis have been discovered by the use of cultures grown in the incubator. We feel sure that this new branch of our laboratory work will justify the expenditure of time and money which will be put on it.

One of the diseases with which we have had to deal very frequently during the past years is "utue unene". It has made us feel hopeless, as we had no cure for it, and besides having a high mortality, it was associated with a great deal of fear and superstition in the native mind. It is a hæmorrhagic disease. Profuse hæmorrhages may occur from the mucous membrane of almost any part of the body, and very often the death is quick. This is the disease which caused the death of our pastor Sekulu Lumbo a year ago now. None of the measures we took to help him were of any avail and three days after the first symptoms of hæmorrhage had appeared, he had literally bled to death. For some years we had suspected that this disease was acute scurvy caused by a lack of vitamin C in the diet. Treatment with orange or lemon juice had met with only partial success. Some of the new research work in America on vitamin C deficiencies has proved that huge doses of lemon juice are needed to restore the body to a state of vitamin C equilibrium again in these acute cases. Sometimes as much as ten to fifteen quarts of the pure juice were needed over a period of a week or more. We had never treated our patients with such massive doses and no doubt this accounts for the lack of response we found in many instances. This term some definite work had been done in our laboratory with tablets used for vitamin C estimations which we brought back with us from Canada. We feel now that we have enough conclusive evidence to label "utue unene" as acute scurvy. We have had some miraculous cures with the use of large quantities of lemon juice.

Francisco, a young man of about thirty years of age, came to the clinic one day with "utue unene". He was a desperate case. He had lost so much blood that his hæmoglobin had dropped to 30 per cent and still the hæmorrhages continued from nose, mouth, kidneys and intestines. He was started immediately on treatment. After three days in which he drank five quarts of pure lemon and orange juice his hæmorrhages had all but stopped. At the end of a week no further signs of scurvy were visible and by titration his body was in vitamin C equilibrium again. He had taken seven quarts of fruit juice during this week. All of the fungating masses from the mucous membranes of mouth and gums from which the hæmorrhages had been so profuse were healed and no further hæmorrhage appeared from any part of his body. He was literally snatched from the jaws of death. He remained with us another week to regain some of his strength, and then walked home, a distance of ten miles. You may be sure that Francisco and his wife were grateful. They brought a gift of two dollars to the hospital (a large sum for a native) and a few days later he and his wife came with a gift of eggs for our children. Francisco never fails to eat some fresh fruit each day. He tells us that if that will prevent him from having "utue unene" again, as we tell him it will, that he will never be in that bad condition again. A few patients like Francisco scattered around among our villages can do more effective public health teaching than we could do in a long time by educational work. But we try to follow up cases like this with some teaching of preventive medicine in the villages.

A few weeks ago a woman was brought in to us, also ill with this same disease. She too was almost dead from great loss of blood. She was vomiting, so could not take fruit juice by mouth. For the first time we tried injections of lemon juice into her vein. Her response was immediate. In twenty-four hours her hæmorrhages had ceased, her gums were healing, and she was able to proceed with treatment by drinking lemon juice.

The laboratory worker is happy to be able to add her contribution to the medical work for the relief of at least some of the physical suffering of these people of Angola. We feel that our medical work is an integral part of the work of the Church of Christ in this country. We would record our appreciation of the fine co-operation we have had from our native church leaders in Chissamba. It means much to realize that they are wholeheartedly behind us in our efforts. We feel that together we are engaged in the work of the Kingdom in this district.

Editorial

AIR-BORNE INFECTION

IN the early Listerian era the air was thought to play an important part in the spread of infection. Lister recommended the use of carbolic acid sprays in an attempt to sterilize the air about the operative field, but these sprays were inconvenient and uncomfortable and were soon abandoned in favour of the aseptic technique, which required rigid sterilization of instruments, drapings and dressing and meticulous care of the hands of operators and their assistants. For years results which were considered satisfactory were secured, and where secondary infection took place they were assumed to be due to some break in the technique.

In the transmission of communicable diseases stress was also at first laid on the influence of the air. That was a reason for placing communicable disease hospitals in remote places and was also the reason for the terminal disinfection of rooms occupied by cases of infectious disease. Both these practices have largely been abandoned and attention focussed on the patient himself and the human contacts with him. Dr. C. V. Chapin, for years the dean of public health in America, did more than anyone to expose the fallacy of placing reliance on terminal disinfection, and it was he who first had courage to brave public opinion and discontinue the practice of terminal disinfection. He insisted that infection came not only from direct contact with droplets from the infected person's mouth but also, and, more insidiously, from the contamination of hands and through hands the contamination of the nose and mouth. The present technique in communicable disease hospitals is largely Chapin's and practically ignores the air as a potential factor in the spread of infection except in the immediate vicinity of the patient.

The doctrine which exonerates the air as an important vehicle in the transmission of disease has recently been challenged. Refined techniques for the bacteriological examination of air have been developed and virulent organisms can now regularly be recovered from the air of rooms occupied by persons harbouring them. W. F. Wells, at the Laboratories for the Study of Air-Borne Infection at the University of Pennsylvania School of Medicine, has been responsible for much of the new work on the subject. No one can now deny that communicable disease organisms do in fact remain viable and suspended in the air for long periods of time. The vital point to be decided is whether these pathogenic organisms contaminate the air in sufficient numbers to produce disease.

In a recent review of the subject Buchbinder[1] has gathered together the literature on the subject and has come to the conclusion that the air is an important factor in the spread of disease. The arguments may be summarized briefly: First, it is undoubtedly true that the air of occupied rooms does contain organisms from the upper respiratory passages of the occupants. It has been estimated that a child in a scarlet fever ward of a hospital might inhale as many as 30,000 streptococci a day. Secondly, there is some

1. BUCHBINDER, L.: The transmission of certain infections of respiratory origin, *J. Am. M. Ass.*, 1942, **118**: 718.

experimental evidence to support the air-borne hypothesis. For example Trillat and Beauvillain[2] report the infection of ferrets by spraying the air with influenza virus, a situation which, of course, may not parallel human occupancy. Thirdly, there is some epidemiological evidence which is suggestive. However, for the most part this evidence is not conclusive and presents weak points which make it difficult to draw conclusions. Finally, evidence is now accumulating regarding the reduction of secondary infections following the sterilization of air with ultra-violet radiation or by chemical disinfection. Some surgeons have become enthusiastic in this connection. del Mundo and McKhann[3] have recently reported some results from the Infants' Hospital in Boston which are thought-provoking. During a period of six winter months 224 infants were cared for under usual conditions. They were in cubicles, the attendants were masked and required to wash their hands before and after contact with each patient. Another group of 150 infants were cared for in cubicles which were protected by means of curtains of ultra-violet light. That is, above the entrance of each cubicle a source of ultra-violet light was placed which provided a curtain of light sufficiently strong to kill air-borne bacteria entering the cubicle, provided there were no strong drafts. Bacteriological examination of the air of the cubicles protected in this way indicated a substantial reduction in bacteria as compared with the other cubicles. During the 6-month period under study the secondary infection rate among the 224 infants was somewhat over 12 per cent; the corresponding rate for the 150 infants was under 3 per cent.

Among surgeons perhaps the strongest protagonist of the air-borne theory is Deryl Hart. He has experimented extensively with air sterilization in operating rooms. The American Hospital Association,[4] in a special bulletin issued in 1940, concludes that the use of ultra-violet light as a sterilizing agent has a place in hospital practice. It is not recommended that hospital administrators should immediately install ultra-violet apparatus, but in new construction of contagious units and surgical units consideration should be given to the provision of facilities for air-sterilization.

Public health authorities have been slow to wax enthusiastic over this new doctrine. Many are not convinced that the air, outside the 3-foot danger zone around the infected person, does carry sufficient bacteria to produce disease. Many are unwilling, with the evidence at hand, to modify present techniques for the control of infection. It may be difficult to explain all cases of secondary infection in operating rooms and communicable disease hospitals on the basis of contact spread. On the other hand it is difficult to explain equally insidious spread of some infections in any other way. Vaginitis in children's institutions is a good example of this. The ability of this infection to spread is almost as great as measles or mumps, yet it is hard to conceive of it as an air-borne infection.

The conclusion of the whole matter at present would appear to be that further study is needed; but the demonstration of viable pathogens in the air does rather put the burden of proof upon those who say that they are of small importance.

FRANK G. PEDLEY

2. TRILLAT, A. AND BEAUVILLAIN: Essai de transmission aérienne de la grippe au furet par voie pulmonaire ou oculaire, *Compt. rend. Acad. d. sc.*, 1937, **205**: 1186.
3. DEL MUNDO, F. AND MCKHANN, C. F.: Effect of ultra-violet irradiation of air on incidence of infections in an infants' hospital, *Am. J. Dis. Child.*, 1941, **61**: 213.
4. Ultraviolet rays as a sterilization agent in hospitals, *Am. Hosp. Ass.*, 1940, Bull. No. 203.

At a conference in London attended by educationalists from 19 countries a children's charter was drafted embracing the basic rights of youth in post-war construction. The conference adopted the charter as a statement of the basic and minimum rights of all children above considerations of sex, race, nationality, creed, or social position. The charter's six points include: the right of every child to proper food, clothing, and shelter shall be a first charge on the nation's resources; there shall always be available medical attention and treatment for all; there shall be equal opportunities and full-time schooling for all; and religious training shall be available for all children.—*J. Roy. Inst. of Pub. Health & Hygiene*, 1942, **5**: 89.

Editorial Comments

The First Commandment in First-Aid

Within the last two years the demand for training in first-aid has increased beyond computation. Books and other publications on it are appearing in large numbers and it is safe to say that no city or town of any size on this continent is without numerous and increasing first-aid classes in schools, factories, and in civilian protection organizations. The army too has taken it up to an extent hitherto unheard of.

This is an entirely desirable state of things. Even if the threat of air raids was not constantly in our minds there is still great value in a widespread knowledge of first-aid methods, and there can be nothing but encouragement of the movement. At the same time experience shows that enthusiasm to learn and practise first-aid must be kept within proper bounds. The first-aider must realize his limits, and must never exceed them. That is the first and great commandment in his work. There is plenty for him to learn within these bounds. Indeed, we feel that medical men generally could pick up useful information here and there in a first-aid course. After all, it is largely a combination of physiology and commonsense. Of the former we can never know too much and without the latter the most profound knowledge may be of no avail.

H.E.M.

Men and Books

SEVENTY-FIVE YEARS OF THE ASSOCIATION*

BY H. E. MACDERMOT

We may do one of two things about a 75-year span of life; either commemorate it as something worthy of note, or use it as an opportunity to review the events of the period. Merely to win to such an age may be a distinction no more than passive in character. To be able to show that the time has been profitably spent is the only distinction of real account. If it can also be claimed that with the passage of time vigour has not been lost but is even increasing, then the distinction becomes notable.

Our Association has passed through 75 years of uninterrupted existence: not perhaps unchecked, nor without periods of difficulty and threats of failure; these things we have known. But there has been no break in the continuity of organization. How profitably has our time been spent? And what evidence is there of increased or even unimpaired vigour?

OBJECTS OF THE ASSOCIATION

First, we must be clear as to the objects of the Association. These are described in our Constitution, but I think that we may also well recall them as set forth by Dr. Tupper, the first president, in his opening speech at the organization meeting in 1867. Dr. Tupper felt that the leading objects of the Association were:

> "To protect the health and lives of the people of this Dominion from the unskilled treatment of incompetent men, and to provide in the most effectual manner for the due qualifications of the members of the profession so important as our own."

What have we added to that? We have widened the program in detail no doubt, but there still will ever remain before us the main object of guarding the health of the people by maintaining the highest medical standards.

With this in mind it may be of interest to look back at some of the developments in the life of the Association.

ORGANIZATION

First, perhaps, there is the actual organization of the Association. It might seem that this should be subordinated to the strictly professional aspect. But history has something to tell us on this point. Actually, there were two abortive attempts to organize a Canadian Medical Association before the third and successful effort in 1867. These failures seem to have been mainly due to weakness of organization.

Even after the Association came into being it suffered two definite threats to its life; the first in the early '90's, when its vitality ebbed so low that a motion to disband was considered. The second was at a period which has a much more immediate interest to ourselves. This was during the war of 1914-18, when only a skeleton organization was maintained, and indeed, for two years no regular meetings were held. The one bond which remained intact was the Association *Journal*, and that we owe to the devotion of a few members, notably Dr. Maude Abbott, Dr. G. G. Campbell, and Dr. A. D. Blackader.

Even after the war, however, the weaknesses in our structure were all too evident. Again it was mainly a matter of organization. The spirit of the members was excellent, but the Association was in debt, its relation to the Provincial medical bodies was weak and ill-defined, and there was no administration of a permanent or full-time nature.

It cannot be said that the magic of reorganization caused all these troubles to vanish immediately. But they were overcome soon enough to make the occasion of their being faced (the

* Prepared for the annual meeting of the Canadian Medical Association at Jasper Park, June 15-19, 1942.

Halifax meeting in 1921) one of the most important and encouraging in our history.

From this point the expansion of the work of the Association has been notable. Perhaps the most significant development in the last twenty years has been the bringing of all the Provincial medical units into a single Federation. This cannot be described in detail here, but it should be looked upon as an achievement of national scope, and one that reflects all the advantages arising from unification. It was brought about only by severe and protracted labour. The barriers of Provincialism, of passivity, and even of frank opposition, had to be dealt with. Only patience and statesmanlike management could have succeeded against these. The credit due to those responsible for this work is of a very high order.

These are the accomplishments in organization. Their strength will be severely tested in the future.

Regulation of Medical Practice

What else have we done? We have steadily maintained high standards in our profession, The relation between the technical aspect of medicine and the regulation of medical practice is extremely close. A notable achievement in this respect has been the bringing about of uniform licensure in Canada.

Here again the story is a long one. It is enough to say that it illustrates clearly the fundamental difficulties arising from Provincial individualism, and the patience and skill required to overcome them. The Association played its most active part in the affair during the first few years of its life. A great deal of hard labour was expended, but beyond keeping the subject before the profession little was accomplished. Later, Sir Thomas Roddick assumed the task of engineering the necessary legislation through many years of opposition. To him is rightly ascribed the credit for an accomplishment of high merit and lasting value.

The Journal

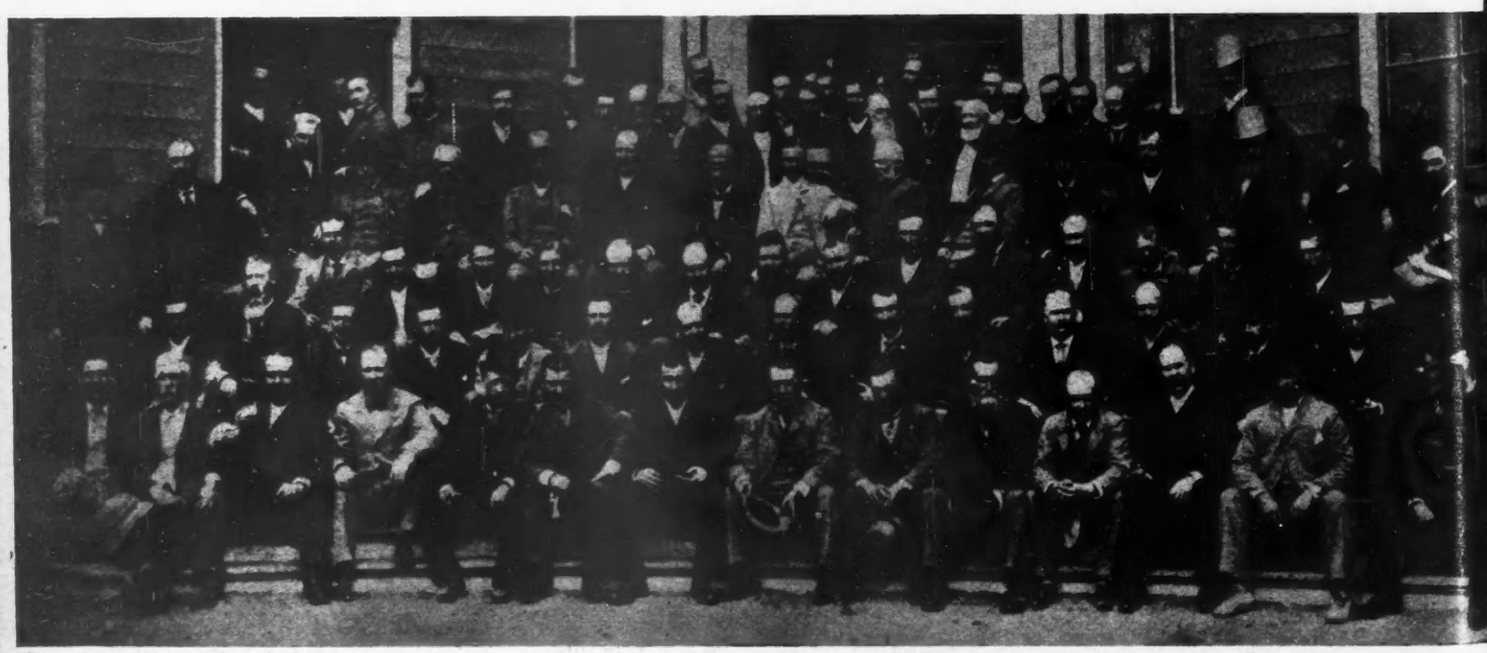
Our *Journal* is one of the most encouraging and pleasing achievements of our Association. That the Association should have a Journal to record its activities and aid in its work might almost be taken for granted, but there is a great difference between a mere record of business and a medical journal.

We were fortunate in having men to develop the *Journal* who were peculiarly suited to the work, particularly Sir Andrew Macphail, the first editor, and his successor, Dr. A. D. Blackader. These men gave of their best, with practically no monetary return.

Consideration has been given in recent years to the idea of a weekly publication, but there are difficulties of a serious, though not insurmountable nature. At present the *Journal* keeps up a good standard, and no change should be made without reasonable expectation of improvement.

Post-graduate Teaching

The Association has in the last twenty years devoted much thought and effort to post-graduate lectures. Beginning in a small way in 1925, the idea was in that year taken up by the Sun Life Assurance Company, from whom the Association received a liberal grant for a year's post-graduate lecturing throughout the Dominion, all lecturers of course being provided by the Association. This most generous help was forthcoming for seven consecutive years, at the end of which period the grants could not be continued.



Courtesy of Dr. Heber C. Jamieson

TWENTY-SECOND ANNUAL MEETING, BANFF, 1889.

It was a completely successful piece of work. In those seven years more than 800 addresses were given throughout the Dominion, and appreciation of the work was unanimous.

THE HOSPITAL SERVICE DEPARTMENT

The Sun Life Company was also responsible for the establishment and maintenance of a Department of Hospital Service, a yearly grant for which has been provided since 1927. The obvious value of the work of this Department is very generally acknowledged.

NUTRITION AND PUBLIC HEALTH

The Canadian Life Insurance Officers' Association has from time to time made beneficent grants to be devoted to the following objects: Nutrition, Publicity and Health Education, Periodic Health Examinations. A great deal of work on these objects has been carried on by the Association, particularly in regard to promoting studies on nutrition, and in the general diffusion of knowledge on this subject. A series of lectures was given by lecturers of high standing, and a very large number of pamphlets of great practical value was distributed.

Recognition of the profession's responsibilities to the public in matters of health education has by this assistance been given practical expression in the form of definite programs of instruction through various channels of publicity.

THE OSLER SCHOLARSHIPS

Mention should also be made of the establishment through the generosity of a group of Montreal men, of two scholarships in memory of Sir William Osler. These are granted every three years to two deserving younger men selected by the Montreal General Hospital and the Royal Victoria Hospital, Montreal.

ORATIONS

Three special Orations have been established by the Association, in honour of Lord Lister, Sir William Osler, and Dr. A. D. Blackader. These are delivered triennially, and are so arranged that only one is given in any one year.

CANCER

Whilst the Association engages in no definite scientific work itself, attention should be drawn to the part it has taken with regard to the problem of cancer. It has been extremely active in the enlightenment of the lay public in this matter, and its Committee for Cancer Control deals with the important details of publicity and dissemination of information regarding the disease.

Along with this it should be mentioned that our Association was directly instrumental in bringing into being the Associate Committee on Medical Research as part of the National Research Council. This committee, with its subsidiaries, is playing a vital part in scientific research associated with the war.

ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA

A development of major importance in Canadian medicine has been the establishment of the Royal College of Physicians and Surgeons of Canada. This is an entirely independent body, but our Association was directly responsible for bringing it into being. Its influence in maintaining high standards of medical work is steadily increasing. It is likely also that the College will be called on to take an important share in the matter of certifying specialists if and when health insurance comes into force.

HEALTH INSURANCE

In recent years the subject of Health Insurance has assumed supreme importance to our profession. It has become clear that the responsibility for medical care of the people is going to be shared to an increasing extent by the Government, just as has been done in other countries.

This development reaches to the very roots of our professional life, and we must be prepared as a profession to take our part in directing its course. If our profession does not now realize that it is faced with changes in the practice of medicine of the gravest nature, it is not because the Canadian Medical Association has not done its utmost to warn and instruct in this respect. The Committee on Medical Economics has formulated with great care the principles which should be borne in mind, and the Association has sponsored at considerable expense the preparation of a series of articles on Health Insurance by a trained and experienced actuary. These have been published in the *Journal* and are available separately.

The Association's standpoint in Health Insurance is clearcut, and support of it is unanimous. It need hardly be pointed out, however, that there are large numbers of medical men outside of the Association, for whom it cannot speak. This is unfortunate in more than one respect, but it is specially so with regard to this matter. If, as is hoped for, the Government is to look to the profession for advice in the fashioning of legislation in Health Insurance, it will be because it feels that it is listening to the profession as a whole, rather than to a section. However, as things are, it can be urged that members of the Association inform themselves as fully as possible of the problems and issues at stake. The problems are many, and the issues are grave. We have to bear in mind not only the interests of the patient, which must ever be protected, but our own principles and rights. These must never be sacrificed, but we should be prepared to adapt ourselves to changing conditions.

It is with this background of achievement and these objectives of endeavour that our Association returns to meet in the West. It is 53 years since the Association paid its first visit to the West. That meeting was held at Banff, under circum-

stances sharply different from the present. Our problems then were domestic only. Now, as part of our country, we are involved in the agony of war. The services of the Association have been offered to the Government freely and spontaneously, and we have gladly responded to every request for assistance.

May there be peace before our next meeting!

Association Notes

Medicine and the Nation*

BY GORDON S. FAHRNI, M.D., Ch.M., F.R.C.S.(C), F.A.C.S.

Winnipeg

The Constitution of the Canadian Medical Association calls for a Valedictory address by the retiring President. I have no doubt that the purpose of this address is:— (1) To inform the members on the deliberations and activities of their Association during the preceding year. (2) To pass on from the retiring officer suggestions and recommendations growing out of his observations and experience as a member of your Executive for at least the previous two years.

The reports to Council of your Executive and standing Committees cover fairly fully the year's activities and anyone reading these reports will be struck, I am sure, by the number and varied character of the subjects handled in the interest of your Association.

I have not the time to go into detail on the subject matter of all these reports, but I do want to say that two of them call for special consideration, and as such for the past year have dominated, to a large degree, the agenda of your Executive and some of its subcommittees. I refer to our co-operation with the Department of Defense of the Government of Canada in assisting to provide medical personnel for the fighting forces, and with the Department of Pensions and National Health of the Federal Government in the study of departmental health proposals for the country. Either of these subjects would provide quite enough material for this address, but the time factor of my programme assignment does not permit me to deal at length with both, so I have chosen the latter, in the hope that I may contribute in assisting my professional brethren to grasp the significance of this great issue, and to suggest to them that the future of our profession seems destined to rise or decline with the success or failure of this movement.

For the past fifteen years, your Association has been interested keenly in the question of Health Insurance, the spearhead of which has been your standing committee on Medical Economics. At the Annual Meeting in 1934, your Council adopted certain principles, thereby stating our attitude on this subject, and at the Annual Meeting of 1937 some amendments of these were made. At the Annual Meeting in Winnipeg, one year ago, we were told that the Department of Pensions and National Health was considering and studying health proposals for the Dominion. Last September your Executive Committee were invited to sit in with the Minister and his deputies at a meeting the following month and a full day was spent with them in Ottawa, considering and discussing these health proposals. Since then a subcommittee of seven, chosen from the members of your Executive, have met frequently, sometimes with Dr. J. J. Heagerty, Chairman of the Advisory Committee on Health Insurance of the Department, and all angles of this subject have been studied.

It is a pleasure to acknowledge the courtesy of the Minister, the Honourable Ian MacKenzie, in making available to us all the material prepared on this subject and inviting your Executive to meet with him and discuss freely the problems arising therefrom. We appreciate, too, the co-operation of the Deputy Minister, Dr. R. E. Wodehouse and of Dr. J. J. Heagerty.

Perhaps, we might now discuss the reason for all this agitation about Health Insurance, in order that we may decide on its merits and demerits, and whether or not we as a profession should support the movement. If we agree to support it, to what extent should our efforts be in the direction of mere passive support, which really amounts to lack of resistance, or of active co-operation with Government authorities, even to the extent of giving some constructive leadership and advice as to how health services should be applied?

I believe it is safe to say, that advances in medicine over the past few decades have made the prevention, investigation and treatment of disease much more intricate and complicated than formerly, all of which has increased greatly the cost of diagnosis and treatment. This burden has been getting steadily heavier for the low-income group, with the result that many are unable to carry it and various plans and schemes have evolved to meet this situation with a view to providing at least a fair service. The indigents for many years have had hospitalization provided by the State, and medical care, both at home and in hospital, has been provided gratuitously by the medical practitioner. These people indeed have fared very well, but is this extra burden fair to our profession?

The low-income group, which represent perhaps the backbone of the nation, have been trying to pay their way, but have found the sudden descent upon them of a severe illness too much to carry. Only too often this has resulted in inadequate investigation and inadequate treatment, much to the disappointment of the medical attendant. In trying to improve their position, they have resorted to community effort, resulting in various health schemes being set up here and there across the country, most of which aim at nothing better than a partial service, but have filled a gap for the time-being, even though sometimes quite inadequately. Some of these health plans have been supported by the Provincial Governments, notably in the Prairie Provinces, where municipalities have employed physicians on a salary basis. There has been an increasing demand by the urban centres, also, for some form of health insurance, so that we find plans coming into operation all over the country. In several Provinces different plans, some with rather a large coverage of people, have been operating for several years, and the number of these is steadily increasing.

Let us take a look at the result of the "Gallup Poll", released by the Canadian Institute of Public Opinion, Toronto, April 8, 1942, which suggests that,—"between seven and eight out of every ten Canadians are in favour of a National Health Plan for medical care and hospitalization, sponsored by the Government". One of the questions used in this survey was worded like this: "If the Government should start a National Health Plan, would you be willing to pay a small part of your (or your family's) income every month so that you and your family would receive medical and hospital care whenever you needed it?" This question was put to all types of Canadians, men and women, rich and poor, from coast to coast, and here is the National answer.

Would be willing.....	75 per cent
Would not be willing.....	18 per cent
Undecided.....	7 per cent

Other details of the poll are very illuminating, but the meat of the report is that at least 75 per cent of the people of Canada want some form of Health Insurance according to the "Gallup Poll" method of obtaining information, which has been shown over and over again to be, at least, fairly accurate. What would be your reaction to the above report if you were a member of the Government in Ottawa?

During the past few months, the Divisions of your Association have co-operated with your Executive in sending out a questionnaire on Health Insurance to all

*Valedictory Address by the President at the Annual Meeting of the Canadian Medical Association at Jasper Park, Alberta, June, 1942.

practising physicians in Canada. The results of study and compilation of answers, so far received, are predominant in favour of cooperation with the Government in some plan of Health Insurance for the whole country.

In Public Health and Preventive Medicine the medical profession has been too inactive. During the rapid advance of this branch of medicine, public funds have been necessary to meet even a part of the need and Governments, in providing these, have organized Departments of Health, one in each Province, and these in turn have proceeded to develop, each as an arm of the Government, sometimes controlled by a lay Minister. The Minister employed whatever number of medical men he wished and the Department functioned on this basis, not as a part of the medical profession, but as a unit in itself. This seemed a natural evolution, no doubt, but it is unfortunate that our legislators failed to realize that no efficient coverage in Public Health can be given without close and harmonious co-operation between the medical practitioners and the Government agency. This in turn means that the physician, who goes into a home, should cross the threshold, not only as a physician to treat a sick member of the household for which he was called, but also as the family doctor who would survey the whole household background, housing conditions, physical fitness, and state of nutrition of the members of the family, a preventable error in which may be the cause of his patient's illness. It is he, who while on the spot, an agent of the Government as well as being the family physician, should investigate the physical fitness of all members of the family:

1. Their state of nutrition, and if this is poor, the question of diet and housing conditions would be taken up with the heads of the family.

2. Specific physical defects, such as septic tonsils, carious teeth, enlarged lymphatic glands, and, perhaps, a persistent cough, would be carefully investigated and remedial measures carried out, in time, perhaps, to prevent some form of arthritis, or an advanced stage of pulmonary tuberculosis, or, still worse, infection of other members of the family.

3. Susceptibility tests for and immunization measures against such infectious diseases as diphtheria and scarlet fever would be part of his routine and such other measures as seem necessary for the physical, mental and moral development of all members of the family.

There are several reasons that come to mind why the family physician rather than the salaried Government official should carry out the program just mentioned. The family doctor is familiar with the background of his flock and enters as a trusted friend and would be expected to receive full co-operation from the household, whereas, the Government official, not always a doctor, comes in, usually a stranger, and is looked on somewhat as a police officer, which has the effect of developing in the household, reticence and reluctance to co-operation, all of which makes efficiency impossible. It is hardly necessary to state that the rôle just outlined for the general practitioner would call for close co-operation with the Department of Health; indeed in this field, perhaps more than any other, a close hook-up between the profession and the Department of Health of the Province is paramount in any plan of Health Insurance. I am convinced, also, that any plan of Health Insurance that fails to feature prominently the application of sound, far-seeing principles of Public Health will fail to meet one great challenge of the day. I would exhort my profession to insist on including in any proposed health plan, a program which would prevent in the future many of the diseases we see today, and carry out remedial measures for curable disabilities, that so many of our people carry about, with no thought of treatment because of ignorance, fear or lack of monetary means.

If anyone here should feel that the people of Canada enjoy a high standard of physical fitness, I would refer them to the result of the medical examination of the first fifty thousand trainees carried out, and the report released by the Department of War Services of the Federal Government. Just over 38 per cent of these young men, in their early twenties, more than one in three, nearly two out of every five, were found physically unfit for front line service. It is true that many of these have comparatively minor and curable defects, but what is being done about remedial care, where it is possible by such to raise their category if not sufficiently high for front-line soldiers, at least enough to make them useful citizens in the field of industrial endeavour, or other useful walks of life?

Many countries of Europe for years have conducted physical fitness campaigns. This movement reached its peak in Germany and Russia, and was not confined to military drill and exercises but was designed to improve the physical, mental and moral development of the youth of the country. The program included a place of importance in the schools, for nutritional as well as physical and general educational effort. In 1941, Australia passed a "National Fitness Act", and funds were provided by the Government to implement it.

I am informed that those who are interested in the field of physical education in Canada and, among them, men associated with universities, are urging that the Dominion Government, through Act of Parliament, establish a Central Council on Physical Fitness and provide a fund to enable the Provinces to set up Physical Fitness Councils, for the establishment of a program along lines similar to those which have been in effect in European countries for years.

I have stressed the importance of Public Health, as I see it, in any plan of Health coverage for the nation because I am convinced that the medical profession should take an increasing responsibility in all its branches, without which no satisfactory progress will be made.

I should like to discuss now, in brief only, a few other points that must be considered in any useful plan of Health Insurance.

The application to medicine of scientific discoveries of the past two or three decades has increased our knowledge of and made it possible to understand much more clearly, the pathological processes underlying many diseases which formerly were treated empirically. The result has been a drop in the morbidity and mortality rates and an increased expectancy of life, so that the tables of longevity today compare very favourably with those of even three or four decades ago and I am optimistic enough to believe, that when the possibilities of preventive medicine are harnessed, a still better showing will be forthcoming.

The municipal and other Government authorities find it hard to believe that the increased cost of the hospital care of an indigent is justified. Much of this increase is due to what we might term extra, or special, services, both from the investigative and therapeutic point of view. In the former, laboratory service including serological and x-ray facilities, shows up prominently in adding to the cost of diagnosis, while the special equipment required for curative measures, particularly many of the special surgical procedures, are quite costly. What they often fail to realize, is the shorter period of hospitalization, which results in a big financial saving, and the decrease in morbidity and mortality, which cannot be measured in dollars and cents.

The people of the low-income group, who are trying to pay their way, unlike Government agencies, often find it impossible to meet the cost of adequate modern medical care and, not infrequently, I am sure, all of you have found it necessary, because of this, to forego costly investigative measures, which might have assisted materially in the treatment of your patient. Health Insurance for this group offers more than for any other, and this brings us to the question of the income limit, or income ceiling, which should apply to any Health plan for this country.

There are some who feel that no income ceiling should exist, but the weight of opinion seems to favour limiting Health Insurance to those whose income is insufficient to provide adequate medical care. Whether the income limit is $1,800 or $2,400 per year is not so important, but it is important, that all the people below the income level set, should come under the plan and this would include all indigents. In the matter of benefits, the prevailing opinion favours a full coverage including hospitalization. This would include preventive medicine and all medical and surgical care, and the highest service possible should be our objective.

The question of division of work between the general practitioner and the specialist requires some careful study; the best of both must be retained and every opportunity provided for each to steadily increase and widen his

sphere of usefulness to the people. The practice of medicine has developed so widely, that it is quite impossible for any one practitioner to cover competently the whole field, and anything short of competent work is to be deprecated.

With an increased scope in Public Health, requiring a good deal of special knowledge and training and working hours, the general practitioner will find himself increasingly busy and glad to avail himself more and more of the services of men trained in special fields of medicine. The one service should be complementary to the other. The principle of free choice of doctor should be protected so that the patient, in so far as is reasonable, may seek attention from the general practitioner or specialist whom he believes is the most capable. This principle instills confidence in the patient and retains the spirit of friendly rivalry between medical people, which is a needed stimulus to further study and better training.

One word about free hospitalization, which we have experienced to a limited degree in Manitoba, through the agency of the Manitoba Hospital Services. The hospitals like it and so do the doctors, but I have found two defects, which stand out prominently, and I mention them in the hope that some corrective measure may be provided:

(1) The patient's contract calls for payment for investigative measures, only if confined to hospital, so we find our patients asking to be sent to hospital when laboratory work, such as blood counts and x-rays, are required for a diagnosis. (2) Once in hospital, the patient decides to use it as a convalescent home, while members of the family at home go on their vacation.

Either of these tendencies is to be deprecated as the hospitals become unnecessarily crowded and the extra outlay in money is unfair to those bodies carrying the insurance. The whole responsibility seems to be left to the practitioner in charge, and it may be hard for the patient to see his point of view.

If a satisfactory and adequate service is to be given to the people, the doctors must receive fair play. There are three methods of remuneration, fee for service, capitation, and salary, and of these I think we may drop the last, for I do not think that either the people, or the profession, would consider State Medicine. The fee for service for the time being seems to hold the floor, but it is interesting to follow the experience of the medical profession of other countries, many of whom have switched to capitation for general practitioner services, at first unwillingly, but in a short time would have nothing else, and the same has held true in a few localized health units in this country.

From the point of view of the general practitioner, as he takes on a wider field in preventive medicine, there is much to be said in favour of capitation, as this would tend to stimulate his interest in keeping his flock healthy.

In any national health plan, careful consideration should be given to providing clinical material for our teaching hospitals and universities, as it is positively essential, that they should carry on the teaching and graduation of doctors. Perhaps, both these institutions should interest themselves more deeply in post-graduate teaching and graduate training, a problem common to them and the medical profession. Graduate training in hospitals, in special branches of medicine, has been steadily increasing for some years and for this movement I have only commendation to offer. Post-graduate work for the practising physician and some plan of superannuation should not be overlooked.

In summarizing my remarks, I am sure most of you think I am, and must have been for a long time, a dyed-in-the-wool advocate of Health Insurance in some form. I must confess to you, that it is only in the past decade, that I have come, gradually, to realize the importance of meeting this need of our people, which some worthy groups have tried to meet, by pooling small monthly payments to provide some partial, or, to say the least, not uncommonly quite inadequate service, while many, financially unable to provide adequate medical care for themselves and dependents, carry on either without it, or because of the charity of the practitioner of medicine. It would seem the need is here; the people wish to have it met and Government authorities are well informed on all angles of the people's attitude. What then is our next move?

The Government of tomorrow may be quite different from the Government of today; we are going through stirring and chastening times. To meet and defeat the onset of totalitarian Nazi and Fascist countries, the British Empire is finding it more and more necessary to wage total war, which means the regimentation of the whole population. Canada is already well along this road and the longer the war continues, the closer to this goal we are sure to drift. This would mean State control of the people, land and industry, capital and labour. After the war the survival of democracy will depend, largely, on whether or not the people can control the bureaucratic sections of Governments and their heads. In reverting to the democratic system of free enterprise, there would be great danger of mass unemployment and political disaster, so I say to you that we must do our part to work out a plan whereby we shall go back, after the war, to a system, in the words of Lincoln, "Government of the people, by the people, for the people".

I have in mind two very good arguments for bringing in a comprehensive Health Plan before this war ends: (1) The sense of security it would give to the people during post-war reconstruction and rehabilitation. (2) The fear, that if the war continues many more years we may find ourselves under a bureaucratic, rather than a democratic form of Government. Dictators and bureaucracies rarely deign to consult, or take the advice of bodies, like the medical profession. We would then be told what to do and what Health Plan we would have! If, however, a satisfactory plan was in operation, perhaps at least something good from it would be retained.

The fate of Health Insurance in this country will be decided by three groups; the Governments (Federal and Provincial), the mass of the people, and the medical profession. The Canadian Medical Association has been called into conference and has been asked to appoint a committee, to work with the Department of Pensions and National Health. Let us rise to the occasion and try in every way possible to see that the best form of medical service will be given to the Canadian people, when, and if, the Governments decide to institute a Health Service for Canada.

I would like to discuss now, in an informal and more intimate way, a problem of policy and administration and make a few suggestions which I hope you may consider and discuss with your Divisional Executives.

Some things we have done, perhaps less well than we had hoped, but there are many things left undone which I feel we well might have done.

It is my firm conviction that the medical profession of this country should give active leadership to everything pertaining to the medical politico-economic welfare of the country and the people should look to them for guidance in all such matters. Are we prepared for this responsibility and have we made it clear to the country that we are ready to accept the challenge?

The purpose of the federation of the Dominion and Provincial Medical Association's was to put into one solid unit the medical profession of the nine provinces of Canada, an organization that could speak for the whole profession in that its executive consists largely of representatives appointed by the various Divisions. Unless all these Divisions are "on their toes" and send instructions to the central body through their representatives only mediocre progress can be expected, but if the Divisions do their part and bombard the Canadian Medical Association Executive with constructive ideas, there is no worthy goal that cannot be reached, assuring the people of Canada sane and efficient leadership and protection in all things pertaining to health, a pillar against which no party-minded political group can hope to stand.

I have tried to intimate that the Canadian Medical Association is only as strong as and no stronger than its Divisions, but to carry the comparison further, the Divisions' strength depends largely on the activities of its District Societies and individual memberships. This then, is a challenge to every medical man to see that he is a member of his Provincial and Dominion medical organization and that he should not stop at being nominally enrolled only, but should exert his intelligent effort in the direction of stimulating his medical organizations to greater achievements.

The General Secretary's Page

A high ranking Cabinet Minister in the Federal Government said to me not long ago, "The Canadian Medical Association doesn't represent the doctors of Canada. I understand only about 50 per cent of the profession are enrolled as members."

It would be well if every doctor in Canada would turn that statement over in his mind. The day will surely come when our strength as measured by membership will be put to the test. You are aware of the fact that Health Insurance legislation is brewing in Ottawa. Fortunately, the Canadian Medical Association has been invited to participate in the preliminary discussions and our views may find expression in the draft legislation which goes before Parliament. But after that, what happens? The Bill receives first reading and then goes to Committee where every one of the more than two hundred members of Parliament is privileged to tear it to pieces, metaphorically. Much more important than the Bill which goes into Committee is the Bill which emerges therefrom. It is in Committee that interested parties are heard and surely no group could be more interested or concerned than the medical profession. The Canadian Medical Association is the only medical body in Canada which can appear before the Committee as purporting to represent the doctors of Canada, and we will be there.

Picture the scene. Your representative is called to the stand. The Chairman asks him three questions:

Whom do you represent?

How many doctors are there in Canada?

How many are members of the Canadian Medical Association?

On hearing the third answer, the members of the Committee relax in their chairs and if they don't all say what the Cabinet Minister said to me, they at least think it.

I well remember a long and interesting conversation I had with the Right Honourable David Lloyd George in England five years ago when he told me the story of the inauguration of National Health Insurance in the British Isles. Here I quote from that interview:

Q. "Did you fear the doctors' opposition?"

A. "No. Before I introduced the Bill, I got Dr. Addison (Minister of Health) to recruit for me 2,000 doctors who agreed to serve under the Act. This was a matter of expediency. The British Medical Association did not have the doctors all solidly behind them and they did not know the strength of my medical army."

Let us turn to another scene. Several years ago, the Government of British Columbia passed a Health Insurance Bill which the medical profession of the Province considered to be unsatisfactory. A plebiscite was taken by the Medical Association and 601 doctors out of 614 who replied said they would not serve under the provisions of the Act. Result—the Act was never promulgated.

When and if we appear before the Parliament of Canada, what a marvelous position we would be in if our representatives could say that they were speaking for *all* the doctors of Canada. Dare we entertain any such hope? Favourable signs are not wanting.

Ontario put on a drive for new members this year and to date has enrolled 746, bringing Canadian Medical Association membership in the province up to nearly 3,000. Moreover, the College of Physicians and Surgeons of Ontario, on the request of the Ontario Medical Association, recently conducted a plebiscite in which every doctor in the province was asked this question:

> "In your opinion, is a compulsory composite fee covering membership in the College of Physicians and Surgeons, the Ontario Medical Association and the Canadian Medical Association, desirable?"

Ballots to the number of 4,553 were sent out. On May 27th, 2,895 replies had been received. 65.9 per cent were favourable. But of even more significance are the following facts:

> 1,555 replies were received from non-members of the Ontario Medical Association and Canadian Medical Association.
>
> 786 were favourable to the compulsory fee.
>
> 769 were unfavourable to the compulsory fee.

Note these figures. Extraordinary, you might say, that a majority of those who are not now members of organized medicine would vote in favour of a plan which would compel them and all other doctors in the province to belong to all three medical bodies.

On second thought, the vote is perhaps not so extraordinary. The pendulum is swinging and it will not be surprising ere long to see the medical profession from coast to coast demanding that it band together as a solid phalanx. Then Canadian Medicine, to the inestimable benefit of both the public and the profession, will stand on a sure foundation.

"How many doctors are there in Canada?"

"How many are members of the Canadian Medical Association?"

On the answers may depend in a large measure the future practice of medicine in Canada.

Medical War Relief Fund

A further letter has been received by the Honorary-Treasurer:

"Dear Dr. Sclater Lewis,

Very many thanks for your letter of March 20th enclosing cheque for £178.10.7 towards the above Fund. It is very kind indeed of the Canadian Medical Association to give us so much assistance. An official receipt is enclosed herewith. I expect you will by now have received my acknowledgment of the cheque for £153.5.8 sent to us on February 10th.

Yours sincerely,
(Signed) G. C. ANDERSON,
Honorary-Treasurer."

April 22, 1942.

Hospital Service Department Notes

Open Formula for Lubricating Jelly Non-injurious to Rubber

The necessity of conserving rubber supplies and of making rubber gloves, catheters and other fabricated articles last as long as possible, has focussed attention upon the use of non-greasy lubricants. Excellent water-soluble lubricating jellies have been available for some time, but we are informed that with the increasing shortage of glycerine and gums it may become difficult for all doctors and hospitals to obtain adequate supplies. With this in mind the Canadian Hospital Council has requested the Ontario College of Pharmacy to investigate the possibility of developing a product which would not require either glycerine or gum, and which could be recommended to the profession and the hospitals. We are indebted to Mr. D. E. MacKenzie, Assistant Professor of Pharmacy in the Ontario College of Pharmacy, for working out a product which has been given clinical trial at the Toronto General Hospital and the Toronto Western Hospital and has been reported as satisfactory.

The following requirements were set up: (1) The proposed jelly should be of moderately thin consistency, be easily spread, possess good lubricating properties and be neither sticky nor greasy. (2) The formula and required apparatus employed in the manufacturing should be as simple as possible and thus the product could be prepared in the hospital dispensaries. (3) The product must be capable of being sterilized by the usual methods and for added protection should contain a bacteriostat. (4) Since the product is applied to rubber gloves it must not attack or react with rubber. (5) The ingredients must be readily obtainable and the cost comparable to that of present products. (6) The product should be stable during manufacture and also during storage. (7) The jelly must necessarily be innocuous to ensure safe introduction into the body cavities.

FORMULA AND PREPARATION

It was found that the following formula would meet these requirements:

Starch	7 oz. 135 gr.
Distilled water	1 gal.
*Sodium lactate (60 per cent)	90 fl. oz.
Mercuric oxycyanide	280 gr.

Dissolve the mercuric oxycyanide (B.P.) (Sol.—18 W) in part of the distilled water, using the remainder of the water to form a smooth paste with the starch. Combine these two portions with the sodium lactate and heat in a steam kettle, or some other device capable of supplying a temperature of approximately 100° C. The heating, with moderate agitation, is continued until a translucent jelly is formed, at which point the product can be at once transferred to suitable containers.

Sterilization.—The product is best sterilized after it has been placed in containers and, following latest approved procedure, can be successfully rendered sterile by autoclaving at a steam pressure of 10 lb. (115° C. or 240° F.) for a period of 30 minutes.

Containers.—Undoubtedly the collapsible tube is the most satisfactory package. Since tin has gone to war almost 100 per cent and alloy tubes cannot be supplied in very large quantities, it might be advisable to standardize, for the time at least, on glass or porcelain jars. These jars could be large enough for a single application only or else packed in larger quantities and resterilized after usage. If jars are used the tops may be conveniently covered by a triple thickness of cellophane, held in place with string or rubber bands and for added protection a further covering of parchment-type paper. Autoclaving may be carried out quite effectively while the container is so wrapped. The package problem may eventually be relieved through supplies of cellulose tubes or lead tubes coated with indium.

COSTS

Based upon the costs of ingredients during the experimental work, it is estimated that the cost of the ingredients would be approximately 50 cents per pound.

Undoubtedly many hospitals will desire to make up this product in their own pharmacies. The hospitals and the medical profession are deeply indebted to Dean Hurst and to Professor MacKenzie for their work in developing this above formula for lubricating jelly.

All communications intended for the Department of Hospital Service of the Canadian Medical Association should be addressed to Dr. Harvey Agnew, 184 College Street, Toronto.

* Sodium lactate is available commercially as a 60 per cent solution from Merck & Co. and other sources.

Correspondence

The Anæsthetist

To the Editor:

In Hamilton there has been some publicity over four anæsthetic deaths which required a coroner's inquest to bring out certain facts in connection with these unfortunate occurrences. There was perhaps more publicity than there should have been and the reaction of the public has been unfortunate. Many said that the doctor was at fault but the majority seemed to think he was "getting a ride".

Personally I think the average anæsthetist takes his work too casually. I have many times asked an anæsthetist whom I was employing to drop in and see the patient the night before and have a chat over things, in other words give him some confidence. Many patients are very apprehensive and they go into the operating room and a rubber mask is tucked over their eyes, and a strange voice orders them to breathe deeply. They have no idea who the man is or what he looks like. On the other hand the anæsthetists say they are usually called up to give so-and-so an anæsthetic and they may have less than an hour to look into things. Certainly I think that taking a patient toward the heavenly gates is no casual job and should be treated as seriously as the operation which is to be performed by the surgeon.

It has been my experience that one has to coax the average anæsthetist to see the patient the day before an operation and surely this should not be necessary. If it is so important that he should be skilled in his work as brought out in the above-mentioned inquest then should he not become acquainted with the patient before he administers an anæsthetic?

Your very truly,
F. B. BOWMAN.

Hamilton, Ont.,
June 4, 1942.

Special Correspondence

The London Letter

(From our own correspondent)

Students in wartime.—Medical students remain very much the same, war or no war, but there is a spirit of unrest amongst them, obviously concerned with their exemption from military service. In the last war medical students were called up as soon as they were of an age to serve, and the result was a serious shortage of medical practitioners in the post-war years. This time exemption of a sort has been in force since the beginning, and as a result of the most recent regulations all medical students are exempt from the date of their acceptance by a medical school, a quota being allotted for each school.

Taking a long-term view, a first-rate student is going to be of more service to the country as a doctor in post-war times, but unfortunately the short-term view is too often held by the first-rate student and he goes off to serve his country now in a combatant capacity. Already the choice before parents and senior boys is a difficult one, but so far there has not been a serious falling off in the quantity of entries to the medical schools. Some doubt is raised as to the quality—but that is not easy to judge yet. Suggestions have been made that all students should do a minimum of training, get their uniforms, and then go back to their studies, uniform and all. The calling-up age at present is 18½, so by that time most students have passed their premedical examination and have begun their preclinical course. Such preliminary training should not be wasted and of course the wearing of uniform is but a gesture. The same unsteadying influence—to fight or not to fight—would still be there, and it is not helped by the rather curiously worded threat used by certain medical school authorities as regards those students who fail in an examination. To "threaten" with the prospect of military service seems a stupid interpretation of the Government's policy, which is clearly to regard embryo doctors as valuable members of the community.

From another angle this value is being more appreciated in the sense that university and medical school authorities are beginning to be concerned with the health of medical students. At Sheffield, for example, where an optional free medical examination at entrance has been available for some years, it is now announced that in future it will be compulsory. Medical students are to have in addition an x-ray examination of the chest, to be repeated at the beginning and during his clinical years, with a sedimentation rate estimation as well. Not only is this an important step with regard to the care of medical students but it is an interesting, pioneer experiment which will help in regard to the possibility of periodical health examinations for the country as a whole.

Dentists.—Dental students are exempt from military service just as medical students, but entries are falling, not necessarily because of the war, and it has recently been estimated that in about ten years' time there will be a very serious drop in the number of dentists on the register, due to the fact that then begins the falling out of the 7,000 or so who were admitted to the register in 1921 without diplomas. It is, of course, a serious matter, for the course of study means a lag of five years between entry and qualification and if entries cannot be increased speedily the situation will become acute, with no large pool of bona-fide but "undiplomated" dentists available to remedy it.

Suggestions now put forward include immediate lowering of fees and providing more scholarships. As a more slowly-acting policy it is also important to make dentistry more attractive by

raising the social status of the profession and improving the general prospects of the middle-aged dentist. If the nation is to maintain its number of registered dentists—1 per 2,700 of population, half the proportion in the United States—something must be done. But it is quite possible that the greatly increased interest in diet may offer another solution of the problem. Just suppose that national wheatmeal bread, vitaminized margarine, subsidized supplies of cod liver oil, fruit juice and milk, make a real difference to the state of the nation's teeth! Then perhaps the supply of dentists *might* prove too large. At any rate is a nice piece of day-dreaming.

Women service doctors. — How extraordinarily awkward the attitude of authorities to employing women turns out to be in wartime conditions! It has taken months and months before A.T.S. girls have been allowed to serve with anti-aircraft batteries and then how surprised the male superior officers were at the great success they have made of the job. The story as regards medical women is equally stupid. Before the war the Medical Women's Federation learned from the War Office that no women doctors would be wanted in any capacity in the Army. But when the war came women doctors were wanted after all—but with a curious "relative rank", that is no definite commission, although salary and allowances were equal to those of their male colleagues. After a lot of wrangling commissions were granted for service *with* but not *in*, the R.A.M.C. and medical branch of the R.A.F. But the medical Women's Federation is dissatisfied. Women doctors serving have no settled status, they are not members of any service, all because of some curious legal difficulty over the presence of women in "land" forces. The Federation has now advised its members not to accept the commissions in the "Women's Forces" now being offered to medical women, but "to stay put" in the curious state of "relative rank" until the matter is negotiated further. It all seems very odd.

Physical education.—The physical medicine experts have won general approval for their very successful "schools" for turning inferior quality to good material in recruits for the services. That fact gave added interest to an inter-allied conference recently held in London, when representatives of many nations gathered to discuss the wider aspects of the subject. The interest shown by our own Board of Education was most encouraging, for the President not only opened the conference but announced a big development of the school medical service whereby the medical needs of the scholar and the after-school adolescent would be covered in a larger way than at present. Col. J. A. Macfarlane, surgical consultant with the Canadian Forces was one of the speakers and information was pooled from such widely separated countries as China and Belgium, Norway and India, Russia and South Africa.

Committee on medical schools.—As part of the already announced post-war official policy on hospital, special mention was made of the position of teaching hospitals. A committee has now been set up "to inquire into the organization of medical schools, particularly in regard to facilities for clinical teaching and research, and to make recommendations". The Committee is not to be concerned with the medical curriculum but with the general organization of medical teaching in its peculiar relationship with university bodies on one hand and teaching hospitals on the other. Post-graduate education will also be considered and sweeping changes are anticipated.

ALAN MONCRIEFF.

London, May, 1942.

The War

First Canadian Division Medical Society

On January 6, 1942, the regular meeting was addressed by Mr. Rodney Maingot, of Southend Hospital, on "Peptic ulcer", illustrated by lantern slides. He discussed etiology, investigation and treatment, both medical and surgical.

At the February meeting the speaker was Colonel L. C. Montgomery whose address on "The run of the mill cases" as seen in Canadian General Hospitals was much appreciated. He covered the problems associated with chest conditions, the gastro-intestinal type of patients —venereal disease and other common army diseases.

In March the regular meeting was made up of reports from some of our own officers, who had been away, discussing the various courses and hospitals, which they had attended.

The Society had an extra meeting in March at which we were privileged to hear Mr. A. Lawrence Abel, who is senior surgeon of the Gordon Hospital for rectal diseases. He gave a masterly and entertaining talk on common problems of the rectum and illustrated part with his own coloured moving pictures of his abdomino-perineal operation for care of the rectum.

Changes in personnel in past 3 months include: Major C. Gossage (Toronto), returned to England, as D.A.D.M.S. 1 Cdn. Div. Major V. O. Mader (Halifax), promoted to Lieut.-Colonel, to command 9th Cnd. Fd. Amb.—then in April fractured his ankle in a motorcycle accident and was replaced by Major F. B. Bowman (Hamilton). Major J. P. MacInerney (Saint John, N.B.), returned to Canada to command a Fd. Amb. Lieut.-Colonel H. A. DesBrisay (Vancouver), left 9th Cdn. Fd. Amb. to be chief in Medicine, 1st Cdn. Gen. Hosp.—later transferred to Canada. Captain R. S.

Middlebro (Owen Sound), Captain R. H. Stevenson (Montreal), Captain D. W. Sparling (Montreal), Captain R. J. Nodwell promoted to Majors. Captain Middlebro and Major T. C. Gibson returned to Canada to other Divisions.

To compensate for our inactivity as far as war goes—most of the Medical Officers of the Division have been again privileged to be able to take a month's post-graduate course at hospitals of their choosing. All these were thoroughly enjoyed and each man expressed his delight at being able to see some of his own particular branch of medicine again.

Amendments May 13, 1942: Major Gossage is now commanding 14th Cdn. Fd. Amb.

D. W. SPARLING, MAJOR,
Secretary-Treasurer.

War Literature

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University Notes

Acceleration of Medical Training

University of Saskatchewan

The prospect of a joint grant from the Dominion and Saskatchewan Governments to assist students has made it possible to accelerate the medical course. The first year, which is the first year of a five-year course, will open at the regular time, September 21st, and will finish by the end of April, 1943. Our second year will begin on June 1st of each year and classes and examinations will be over by Christmas, which will permit students to transfer to schools whose third or corresponding year begins on or shortly after January 1st. In accordance with this arrangement second year classes are now in operation.

Abstracts from Current Literature

Medicine

Syphilitic Aortic Insufficiency: The Asymptomatic Phase. McDermott, W., Tompsett, R. R. and Webster, B.: *Am. J. M. Sc.*, 1942, **203**: 202.

The authors have studied 2,718 syphilitic patients examined in the New York Hospital during a 4½ year period, relative to the occurrence of syphilitic aortic insufficiency. One hundred patients were found to have involvement of the aortic valves, and nine had aneurysms as well.

Their conclusions are that aortic insufficiency due to syphilis is present in a clinically recognizable form for periods of from two to ten years before the development of symptoms. Approximately one-half of the patients with this form of valvular disease had not developed symptoms referable to it when first observed. The authors believe that adequate therapy prior to the development of symptoms of cardiac failure will result in new prognostic data relative to the duration of life in patients with cardiovascular syphilis. E. S. MILLS

Cardiac Infarction. Shillto, F. H., Chamberlain, F. L. and Levy, R. L.: *J. Am. M. Ass.*, 1942, **118**: 779.

In 50 cases of uncomplicated cardiac infarction an analysis was made of the incidence, time of appearance, and duration of certain signs.

Increase in the sedimentation rate was observed in all but one case. Fever occurred invariably. Other signs were less frequently present.

A rectal temperature above 104° F., a leukocyte count higher than 25,000, or a venous pressure over 200 mm. of water indicated a grave prognosis. Seven of 8 patients showing any one of these signs died within 16 days after the coronary attack.

The level of the sedimentation rate is helpful in the differentiation between anginal pain and cardiac infarction. It is of particular value in cases of infarction with mild symptoms which are not seen by the physician during the first few days of illness. It is not a guide in prognosis. S. R. TOWNSEND

Surgery

Physiology of Gastric Secretion, Particularly as Related to the Ulcer Problem. Schiffrin, M. J. and Ivy, A. C.: *Arch. Surg.*, 1942, **44**: 399.

This is one of a symposium of articles on peptic ulcer. There are many mechanisms which may be concerned in the production of the primary defect in the stomach or the duodenum, but why this defect sometimes develops into an ulcer and other times heals spontaneously is uncertain. One thing is certain, the actual destruction of the tissue results from the proteolytic (hydrochloric acid and pepsin) action of the gastric juice. A large amount of experimental evidence has shown that the corrosive action of gastric juice is of prime importance in the genesis of post-operative jejunal ulcer and that gastric juice is undoubtedly a chronicity factor in delaying the healing of experimental gastric lesions. Mann has expressed the opinion that the importance of acid in the causation of ulcer cannot be overemphasized. The proteolytic power of gastric juice is due not to acid alone but to pepsin in acid solution. Ulceration of the gastro-intestinal tract has never been produced by physiological concentrations of acid in the complete absence of pepsin. The authors conclude that the irritating action of acid and pepsin is the prime factor in the genesis of post-operative jejunal ulcer and is an important factor in the development, persistence and perforation of gastric or duodenal ulcer.

G. E. LEARMONTH

Arteriography of Abdominal Organs by Aortic Injections. Nelson, O. A.: *Surg., Gyn. & Obst.*, 1942, **74**: 655.

Although reference to this subject is rare in English literature there is a moderate amount in the Spanish and French since 1932. Its diagnostic value lies in the x-ray definition of peri- and intravisceral arterial blood supply. This also pertains to normal or degenerative conditions in the abdominal aorta. Eight to 10 c.c. of 80 per cent sodium iodide solution are used with immediate x-rays. Iodism, injury to the aortic wall, and extravasation of the contrast material are sequelæ which have been worked out to satisfactory treatment stage. The details of the procedure may be found in this reference. FRANK DORRANCE

Spondylitis Adolescens—Struempell-Marie Disease. Blair, H. C.: *Surg., Gyn. & Obst.*, 1942, **74**: 663.

X-ray treatment has proved to arrest the progress of this disabling familial disease in 74 per cent of 15 cases with permanent benefit in 67 per cent of these 74 per cent. After experimentation he finds the mast cells surrounding the joints to be fewer in numbers and all of them contain fewer granules of mucoitin sulphuric acid, with the finding of metachromatic substances in the connective tissue of the corium. He hypothecates spondylitis adolescens as a disturbance of sulphur metabolism on the systemic-deficiency basis wherein an absorption of cartilage takes place at the involved joints thus allowing for progressive ankylosis frequently associated with iritis.

FRANK DORRANCE

"Cancer du sein". Macdonald, I.: *Surg., Gyn. & Obst.*, 1942, **74**: 75.

L'auteur base son étude sur l'examen de 2,636 cas tirés des archives du cancer de l'American College of Surgeons. Une échelle de cas aussi élevée, tous rigoureusement contrôlés, permet d'évaluer facteurs d'intérêt général, comme la genèse, le pronostic, et le traitement des cancers du sein.

L'âge des malades atteintes d'un cancer du sein n'a pas une signification péremptoire comme on le croit généralement. Excepté dans les cas inflammatoires survenant en période de gravidité ou de puerpéralité, les chances de guérison sont égales à tous âges. Les meilleurs résultats sont toutefois obtenus entre 35 et 50 ans, les moins satisfaisants entre 50 et 60 ans.

Le facteur le plus constant et le plus apparent dans la genèse du cancer du sein provient de la faillite de fonctions physiologiques à laquelle la glande mammaire est destinée, notamment celle de l'allaitement.

Le résultat final du traitement est amélioré lorsque les lésions sont prises dès le début, mais plus encore en raison de la nature histologique des lésions. Un traitement radical n'est pas contre-indiqué, en lui-même, dans le cas de cancers à longue échéance. Le criterium d'opérabilité réside dans le degré d'envahissement des ganglions axillaires. L'auteurs recommande avec la chirurgie des traitements adjuvants.

PIERRE SMITH

The Diagnosis and Treatment of Cancer of the Stomach. "Le diagnostic et le traitement du cancer de l'estomac." Gray, H. K.: *Surg., Gyn. & Obst.*, 1942, **74**: 487.

Elle est unanime à signaler qu'une cure opératoire du cancer de l'estomac, pris au début de son évolution, est la seule thérapeutique reconnue jusqu'ici efficace. Toutefois, l'auteur constate que seulement 28.9 pour cent des cas qui ont subi la résection de leur tumeur maligne étaient encore vivants cinq ans après l'opération.

L'auteur remarque que la radiographie ou la gastroscopie n'apportent pas toujours des conclusions précises et que, dans bien des cas, des erreurs de diagnostic radiologique ont été commises quant à la différentiation d'un petit ulcère cancéreux, d'un ulcère gastrique présentant de la malignité, et d'un ulcère gastrique bénin.

L'opérabilité dépend de la situation, de l'extension et du caractère du cancer. Le radiologue

Carman a divisé l'estomac en 3 zones: la zone opérable ou pylorique; la zone frontière ou médiane; et la zone inopérable ou cardiaque. Cependant, il ne faut pas considérer avec trop de rigidité cette division de principe et s'adapter aux circonstances.

En cas de diagnostic d'ulcère gastrique, il est recommandé de mettre le patient sous observation et traitement pendant un mois: si l'ulcère est en évolution et le malade jeune, si l'ulcère a moins d'un centimètre de diamètre, si l'ulcère est sur la petite courbure ou sur la paroi antérieure ou postérieure.

Une opération est recommandable si au bout d'un mois, après examen radiologique et gastroscopique, la fermeture n'en est pas complète.

PIERRE SMITH

Obstetrics and Gynæcology

Renal Function Tests in Normal and Toxæmic Pregnancy. Kreiger, V. I. and Norris, N.: *J. Obst. & Gyn. of the Brit. Emp.*, 1941, **48**: 726.

The urea concentration-excretion test is a much more sensitive test than the blood urea test and enables less gross renal damage to be detected during a toxæmic pregnancy. It can also be used to trace the rate of recovery of renal efficiency. The presence of albumin in the urine of a large number of patients whose kidneys had recovered normal function in relation to excretion of urea in tests 2 months after pregnancy, and the persistence of traces of albumin in the urine of many of these patients even 12 months after delivery show that this is an even more delicate means of indicating that the kidney is not completely normal.

A study of the urea concentration-excretion test during and after pregnancy shows that the excretion of urea by the kidney is decreased slightly even by normal pregnancy, but that a marked diminution in renal efficiency frequently occurs in severe toxæmias during the pregnancy. The recovery of normal function takes place often within 8 days and usually within 2 months of delivery, by which time maximum urea excretion is attained. In eclampsia the recovery is slower, the maximum excretory power being regained within 12 months.

P. J. KEARNS

Persistent Functional Corpus Luteum. Black, J., Heyns, O. S. and Gillman, J.: *J. Obst. & Gyn. of the Brit. Emp.*, 1941, **48**: 685.

An account of the microscopic features of the corpus luteum, a fragment of ovary, and the endometrium has been given in an authentic case of persistent functional corpus luteum.

Evidence has been adduced to show that this corpus luteum is different histologically from the premenstrual and degenerating corpus luteum of menstruation. It has been shown that this persistent functional corpus luteum resembles in many respects the corpus luteum of pregnancy, but that the colloid droplets were more numerous and attained a greater size during pregnancy and that a central coagulum was present in the persistent functional corpus luteum and is usually absent in pregnancy.

The endometrium exhibited a typical premenstrual reaction associated with the pregnancy cells of Sturgis. The value of infranuclear or basal fat in the gland cells as an indicator of optimal progesterone activity has been emphasized. It has been shown that the stromal cells in the endometrium had reached a stage of development no greater than that encountered in the endometrium in the late second half of the cycle, despite the fact that the persistent functional corpus luteum had been active for a period of four months.

It is suggested that the term "persistent functional corpus luteum" should be applied to conditions similar to the one described.

P. J. KEARNS

Glomerular Filtration and Renal Blood Flow in the Toxæmias of Pregnancy. Dill, L. V., Isenhour, C. E., Cadden, J. F. and Schaffer, N. K.: *Am. J. Obst. & Gyn.*, 1942, **43**: 32.

Inulin and diodrast clearances have been done on 10 patients with "pre-eclampsia", and 10 patients with "hypertensive disease". "Pre-eclampsia" is characterized by a decreased rate of glomerular filtration, a normal renal blood flow and a decrease in the filtration fraction. Patients with "hypertensive disease" have reduced glomerular filtration and renal blood flow, but an elevated filtration fraction.

In both groups of patients post partum the glomerular fraction tends to return toward normal and in both groups the renal blood flow falls well below the normal level.

Evidence is presented in support of the theory that the same fundamental vascular abnormality is responsible for the hypertensive diseases as for the toxæmias of pregnancy and their sequelæ.

ROSS MITCHELL

Endometriosis. Holmes, W. R.: *Am. J. Obst. & Gyn.*, 1942, **43**: 255.

Eighty patients with proved endometriosis occurred in 307 gynæcological laparotomies, an incidence of 26 per cent. Endometriosis is a disease of middle menstrual life with an incidence of 78 per cent between the ages of 30 and 45 years in the reported group of cases.

The majority of the endometrial lesions occurred in the ovaries, anterior and posterior cul-de-sac, and the rectovaginal septum.

The frequent occurrence of external endometriosis, adenomyosis and fibromyomas in the same patient suggest that these may have the same etiology. Belief in the theory of vascular and lymphatic meastasis as the mode of dissemination of endometriosis is expressed.

Dysmenorrhœa, abnormal uterine bleeding, lower abdominal pain, sacral backache and dyspareunia are the most frequent symptoms of endometriosis.

Conservation in the treatment of endometriosis is justified by the end results in the cases reported.

Endometriosis with its riddle of etiology, its devastating effects on the reproductive organs of young women, its unknown factors of prevention, remains a real challenge to every gynæcologist for the solution of these problems.

ROSS MITCHELL

Neurology and Psychiatry

Basilar Invagination of the Skull—So-called Platybasia. Craig, W., Walsh, M. and Camp, J.: *Surg., Gyn. & Obst.*, 1942, **74**: 751.

Basilar invagination of the skull is a deformity of the occipital bone, which narrows the foramen magnum, and of the upper cervical vertebræ, which narrows and flattens the spinal canal. Removal of the bone which is compressing the underlying brain and spinal cord usually will be followed by relief of symptoms. The clinical picture varies considerably. The authors report three cases. In two of the cases associated anomalies of the upper cervical vertebræ were present in addition to platybasia. The symptoms suggested involvement of the upper cervical spinal cord and the brain stem. The neurological signs indicated a lesion of the cerebellum or its tracts in all cases, and in one case each a lesion of the brain stem and a lesion of the spinal cord in the upper cervical region. Operation was carried out in each case, and adhesions between the meninges and inferior poles of the cerebellar lobes and brain stem were present and were freed in all cases. In two cases marked herniation of portions of the cerebellar lobes occurred. Relief from symptoms was striking in all three cases. The characteristic roentgenographic picture of platybasia has been noted in several other patients in whom there were no signs or symptoms of involvement of the nervous system.

FRANK TURNBULL

Spinal Cord Injuries. Analysis of Six Cases Showing Subarachnoid Block. Mayfield, F. and Cazan, J.: *Am. J. Surg.*, 1942, **55**: 317.

Most sound neurosurgical opinion at the present time favours a very conservative attitude in respect to the use of laminectomy in major compression injuries of the spinal cord. The presence or absence of evidence of subarachnoid block, as demonstrated by a Queckenstedt test, is not a satisfactory criterion for operation. The authors point out that obstruction of the subarachnoid space may disappear spontaneously. Cerebrospinal fluid dynamics may return to normal in patients not operated upon in about the same period of time as in those upon whom laminectomy was done. Laminectomy is indicated in compression injuries of the cord only if there is an incomplete lesion and the patient is showing progressive loss of function and the loss of function cannot be arrested by closed manipulation.

FRANK TURNBULL

Therapeutics

Vitamin D in the Treatment of Infectious Arthritis. Slocumb, C. H.: *Ann. Int. Med.*, 1942, **16**: 241.

The author states that large doses of vitamin D have been of help in partially controlling the symptoms of infectious arthritis in seven of 14 patients, and in 68 per cent of 25 courses of treatment. Very little effect was seen on the objective findings in the patients so treated. Vitamin D is not a specific agent for the control of infectious arthritis. Exacerbations may occur while the patient is taking large doses of this vitamin. The beneficial effects are only transitory, as a return of symptoms usually occurs after discontinuing its use. There is some risk of renal damage, which is apparently temporary if the administration of vitamin D is discontinued promptly after evidence of toxicity appears, but serious damage may occur. It is not necessary to produce toxic symptoms or renal damage, to obtain clinical improvement.

There is no good correlation between clinical improvement and renal damage as evidenced by retention of urea. However, 11 patients who had normal calcium, two experienced clinical improvement and two did not.

Gastro-intestinal upset was the most frequent sign of toxicity; however, in one case the concentration of urea became elevated without the occurrence of any gastro-intestinal upset. Patients receiving vitamin D should be watched carefully for symptoms of toxicity. Vitamin D therapy should be considered as one of many types of treatment which is sometimes of help in the temporary and partial control of infectious arthritis.

S. R. TOWNSEND

Meningococcal Meningitis: Report of Fifty Cases, Forty Treated with Serum and Ten Treated with Serum and Sulfanilamide. Campbell, E. P.: *Ann. Int. Med.*, 1942, **16**: 694.

Among 40 patients treated with serum there were 20 deaths, including 5 with fulminating infections. In two patients treated with serum and sulfanilamide there were no deaths.

The incidence of certain features, such as multiple cases, recurring attacks and meningococcæmia, as they occurred in this group of patients, is given. Important epidemiological and immunological information may be obtained from a study of these features of this disease.

From the results of this study as well as the reports of others it seems clear that chemotherapy alone or in combination with immune serum is the most effective way of treating meningococcal meningitis. S. R. TOWNSEND

Pathology and Experimental Medicine

Exophthalmometric Measurements in Patients with Thyroid Diseases with some Discussion of Their Significance. Galli-Mainini, C.: *Ann. Int. Med.*, 1942, **16**: 415.

In this paper are presented measurements of the degree of protrusion of the eyes in 126 patients, 13 of whom had non-toxic nodular goitres, 3 had thyrotoxicosis with nodular goitre, 58 had thyrotoxicosis with diffuse goitre; 18 had myxœdema following surgery to the thyroid, and 34 had spontaneous myxœdema.

For control the eyes of 50 normal persons were measured. The upper limit of protrusion in these normals was found to be 17.5 mm. Therefore, any measurement greater than this was considered to be exophthalmus. In all these patients who had been recognized to have had exophthalmus during the active phase of their disease some degree of it was persisting at the time thereafter when measurements were made. Patients who had no history of exophthalmus during the course of their disease gave measurements within normal limits when examined by the author. The usual forms of treatment for Graves' disease seem incapable of completely abolishing exophthalmus.

The thyrotropic hormone is considered not to be the sole factor in the production of exophthalmus, but rather one of several.

In the production of œdema in the orbit, it is believed that extraocular muscles play an important rôle. Under conditions of health, they, through the tension they exert, maintain a certain intraorbital tissue pressure which is necessary to normal circulation in the orbit. In thyrotoxicosis, due to the weakness of the muscles which accompanies it, there is a drop in orbital tissue pressure which permits the escape of fluid from the vessels. This state of affairs is also aggravated by other œdematogenic factors.

S. R. TOWNSEND

Revue Canadienne de Biologie, 1942, 1.

Le numéro 4 de *la Revue Canadienne de Biologie*, vient de paraître. Il contient deux articles en anglais et cinq articles en français. Un article venu directement de France apporte un travail du Collège de France sur un état particulier des substances colloidales, dont la connaissance est indispensable à l'étude de la matière vivante, (Madame Dobry). Trois articles apportent des travaux effectués partie en France, partie en Amérique. Ce sont ceux de M. et Mme Leblond, sur la correction de certaines déficiences du lait écrémé bouilli; de M. Leblond, sur l'évolution de l'iode, dans l'organisme, étudiée par les nouvelles méthodes de radioactivité artificielle, établies dans les laboratoires de synthèse atomique de M. et Mme Joliot Curie; enfin, de M. Wurmser, sur une condition essentielle à la conservation du sang dans les réserves de guerre.

D'autre part, MM. Roger Barré et A. Jacques étudient l'action hypnotique de certains mèdicaments nouveaux; M. S. A. Komarov, les propriétés qu'ont certains extraits de muqueuse de l'intestin de provoquer la sécrétion gastrique. Et M. J. Miller expose le cycle extrèmement curieux d'un parasite de la truite qui passe sa vie successivement dans la truite, dans un canard (le Plogeon à collier) et dans un mollusque aquatique. . . .

Une abondante bibliographie de livres nouveaux de biologie forme les dernières pages de la revue. J. SAUCIER

Hygiene and Public Health

Studies on Influenza: Antibody Level: Isolation of Virus. Hare, R., Auger, W. J. and McClelland, L.: *Canad. Pub. Health J.*, 1942, **33**: 72.

This study is based on the assumption that there is a distinct correlation between antibody level and susceptibility to influenza A virus infection. Some experiments are described on the titration of antibody levels against influenza A. These indicate that a high proportion of the population is normally susceptible to influenza and that following infection the antibody titre rises very markedly.

The main part of the paper is devoted to a description of the results of the inoculation of 98 persons with the complex vaccine of Horsfall, Lennette and Rickard (a mixture of influenza A and canine distemper viruses). Horsfall *et al.* had reported encouraging results from the use of this vaccine in institutional populations. The authors of this paper did not have a proper opportunity to assess the value of the vaccine clinically, since an epidemic of influenza broke out almost the same day the vaccine was given. Of the 98 persons vaccinated 13 became ill during the 14 days following the vaccination. There were, therefore, 85 subjects left who did not become ill during this period. Forty-one of these were studied as to their antibody level before and after vaccination. The response proved variable. Some showed a well marked increase in the titre of their antibodies; others showed very little response. It is estimated that about half the group were rendered immune. The disadvantages of this method of vaccination are listed as follows: (1) 50 per cent of subjects do not appear to be immunized. (2) The immunity conferred is probably quite temporary. (3) The immunity applies to influenza A and not to influenza B and other strains at present designated as influenza X. FRANK G. PEDLEY

The Influence of Vitamin B (Complex) Surplus on the Capacity for Muscular and Mental Work. Simonson, E., Enzer, N., Baer, A. and Braun, R.: *J. Indust. Hyg. & Toxicol.*, 1942, **24**: 83.

The experimental work described in this article deals with 23 persons who were subjected to various fatigue tests. After establishing normal curves on each for each type of test, 12 of the subjects were given 9 tablets a day of Betolake'' in addition to their ordinary diet. The 8 tablets contained 6 mgm. of thiamin, 80 mgm. of nicotinamide, 8 mgm. of riboflavin and 0.3 mgm. of pyridoxine hydrochloride. Eleven subjects were used as controls and were given 8 placebo tablets of the same appearance and taste as the Betolake tablets.

The muscular fatigue tests showed no greater improvement in the subjects given the B surplus than in the controls.

The fusion frequency of flicker was used as a test for fatigue of the central nervous system. The authors say the reaction is decreased in fatigue of the central nervous system and is not influenced by effort or by training. This test did show a well marked difference in the two groups. Of the 12 subjects given the B surplus 5 showed a pronounced increase in the rate of flicker necessary to produce fusion; 3 showed a moderate increase, and 4 showed no change. In the 11 control subjects there was practically no change. So far as subjective sensations were concerned all of the group receiving the B surplus recorded improvement, only one of the control group.

The authors believe, therefore, from this experimental evidence that a favourable influence on the capacity for all types of work characterized by fatigue of the central nervous system may be expected in the majority of people if a considerable surplus of vitamin B complex is added to the normal diet. FRANK G. PEDLEY

Is There Need for the Fortification of Milk? McCollum, E. V.: *Am. J. Pub. Health*, 1942, **32**: 80.

McCollum emphasizes the value of milk as the one food for which there is no effective substitute. For many years health officials, with a view to safeguarding milk against dangerous human contacts which may infect milk and bring about epidemics, have urged the adoption of ordinances prohibiting the subtraction from or the addition of anything to market milk. This standard was first relaxed when market milk was permitted to be fortified with vitamin D. There was considerable justification for this, particularly as vitamin D is notably lacking in ordinary foods and notably necessary for growth and development.

With the discovery of other protective food elements the temptation to add them to milk and other food products became very strong. There are two great fields for the exploitation of vitamins—through the drug trade and through the food industry. It is said that 10 years ago retail sales of vitamin preparations totaled around 2 million dollars a year (U.S.A.). In 1939 retail sales in drug stores reached the 100 million dollar mark. In the food industry the addition of vitamins was inhibited somewhat at first by the cost; but the cost has now been reduced and we are now meeting with proposals to enrich cereals, fats and oils, and even sugar.

Milk is notably low in iron, copper, manganese, ascorbic acid and vitamin D. It has been proposed to add carotene to milk to make winter milk look like summer milk and increase its vitamin A value. In one city a milk is being marketed with the approval of the local health department, which is fortified with 5 vitamins and several minerals.

McCollum believes it is uneconomical to take foods apart and then recombine certain components. If people plan their diets wisely they will get the necessary variety without having to resort to fortified foods, and at a lower cost. Another consideration which makes the fortification of milk questionable is the cost of supervision. It is generally assumed now that a food product like milk is safe and of the advertised quality. In order to assure the public that this is so the cost of inspection and analysis would certainly increase.

On the whole, McCollum is willing to agree to the fortification of milk with vitamin D, but does not recommend any other additions.

FRANK G. PEDLEY

Obituaries

Dr. Joseph Patrick Armstrong, of Ottawa, died on April 4, 1942. Dr. Armstrong was born in Ottawa, in 1902, a son of the late Patrick Armstrong and his wife Jane Warusck. He was educated at Ottawa Collegiate and graduated from Toronto University in 1927. He completed his internship in hospitals in New York, Philadelphia and Ottawa. Dr. Armstrong was attached to the Ottawa Civic Hospital staff for some years and was a member of the staff in charge of public ward patients.

Dr. Samuel Harvey Corrigan was born in Milton, Ont., and graduated in Medicine from Trinity College in 1896. He at first practised in Minnesota and located at Lampman, Sask., in 1910, where he conducted a busy general practice until ill health forced his retirement last autumn.

Dr. Corrigan represented the finest type of general practitioner. In spite of the immediacies of general practice he kept himself well informed in the progress of all branches. In his small hospital he conducted up to date investigation and did his own surgery. He became a Fellow of the American College of Surgeons in 1927. He maintained a fresh and progressive point of view throughout his long career, and contributed several articles to the Canadian Medical and other journals. Within a few hours of his death he was busy preparing a case report for publication.

He is survived by his widow, one daughter, Miss Lorraine Amos, and one son, C. E. Corrigan, F.R.C.S., Capt. R.C.A.M.C. who is now on active service overseas.

Dr. Alphonse Ferron, of Montreal, died in his 58th year during the first week of June, 1942. Dr. Ferron was born at Ste. Flore, Champlain County, Que. After completing his classical course at the Three Rivers Seminary, he studied at the University of Montreal (M.D., 1909) and later went to Paris. He specialized in the surgery of children. He was a surgeon of the Notre Dame Hospital for many years and later was appointed head surgeon in his specialty at the Ste. Justine Hospital. At one time he was offered an appointment at the Mayo Clinic in Rochester, N.Y., but decided to remain in Montreal. He was professor of Clinical Surgery at the University of Montreal.

Dr. Angus James Fraser, chief medical officer of the Workmen's Compensation Board of Manitoba from its organization, died at his residence in Winnipeg on May 23rd. Born in Huron County, Ont., he came west to Virden district in 1879 at the age of eight. Later he taught school in the district, then attended the University of Manitoba and graduated in Medicine in 1900. In 1929 his text book, "Trauma, Disease, Compensation", the result of his many years of experience as chief medical officer of the Workmen's Compensation Board, was published by the Macmillan Company of Canada. It has been accepted as an authority on the extent and duration of disability arising either from accident or disease.

Gifted with good judgment, calmness and firmness of purpose, he filled his position admirably so that he was respected by workmen, surgeons and fellow officials. The medical profession of Manitoba found him always fair and reasonable, even under exacting conditions.

Dr. Nelson P. Grant, died in Woodstock, N.B., on May 28, 1942, caused by a sudden heart attack, a few minutes after he had completed his address to the nurses graduating class of the Fisher Memorial Hospital.

Dr. Grant was born in Southampton, N.B., 69 years ago, the son of the late Henry and Barbara Grant. Educated in country schools and at the Normal School, he taught school for two years before going to McGill University (M.D., 1904) for his medical education. His internships were in the Royal Victoria Hospital, Montreal, and in the Saint John General Hospital. Dr. Grant had few interests outside his profession but his chosen recreations were dear to him, angling especially for salmon, was his delight. Politics at times was an interest and the schools of Woodstock claimed much of his leisure.

As a surgeon N. P. Grant was known throughout New Brunswick and the State of Maine. His success was due to perpetual reading, native ability and dexterity, and careful diagnostic methods and close attention to aftercare. He is survived by his wife and two daughters.

Dr. Grant practised for 30 years in Woodstock, which has been noted for and blessed by excellent surgeons for a long period. The names, N. P. Grant and the late Dr. W. D. Rankin were known for many years as evidence that excellent surgery is possible in smaller towns.

Dr. William Everett Gray died at Milltown, N.B., at his home on May 22, 1942, after a long illness at the age of 56. He was born in Saint John, N.B., and graduated in medicine from McGill in 1907. Internship at the Montreal General Hospital and the Saint John General Hospital followed. He practised in Milltown from 1910 to the time of his death. He was from the beginning of his practice a staff member of the Chipman Memorial Hospital, and organized and served as pathologist in the Prescott Memorial Laboratories in that hospital. He was a past president of the New Brunswick Medical Society (1938), and since 1939 represented New Brunswick on the executive committee of the Canadian Medical Association. At the time of his death he was a member of the New Brunswick Council of Physicians and Surgeons and a member of the Executive of the New Brunswick Medical Society. He was a Founder's Fellow of the Royal College of Surgeons of Canada. He was a high ranking Mason, a skilled golfer and sportsman, keenly interested in dogs. He never married, yet his interest in children was well known and his service on the school board and town council were welcomed by his fellow citizens.

Dr. Gray brought great credit to his town, hospital, and the St. Croix valley by his gift of surgical ability. His surgery covered many fields, partly of necessity and perhaps more by his belief that a surgeon should be at home in many body areas rather than confine his efforts to a restricted specialty. Among his patients were of course the poor and needy, but he also numbered many grateful wealthy ones who sojourned in the summer at St. Andrews-by-the-Sea.

"Bill Gray" gave freely of his time and advice to local, provincial and national medical organizations—where his tenacity, stubbornness, conservatism and loyalty were greatly appreciated. His friends were always liable to criticism—but anyone in trouble found out the kind heart, wide sympathy and practical help which were constantly available and freely poured out by this kindly physician. He will be missed by all of us who knew him as a host, physician, or friend.

Dr. Hugh John Roy Lindsay, of Woodstock, Ont., died on May 16, 1942. Dr. Lindsay was a native of St. Thomas, Ont., the son of the late Mr. and Mrs. Alexander Lindsay. He was born in 1885 and a graduate of the University of Toronto (1906). He had just been appointed M.O.H. for Woodstock last January.

Dr. Daniel Patrick Mahoney died at his home in Saint John, N.B., May 31, 1942. He was born in Melrose, N.B., on June 9, 1874. Educated at St. Joseph's University, Memramcook, and Rock Hill College, Maryland, he graduated in Medicine from the College of Physicians and Surgeons, Baltimore (1905). After practising one year in Labrador, Dr. Mahoney practised for eight years in Rexton, N.B., and then moved to Saint John in 1917 where he had been located ever since. A large general practice, including much obstetrics, occupied his time fully. His popularity with his professional colleagues was the direct result of a jovial nature and a high ethical standard. For some years his health had been uncertain following a coronary thrombosis. His death leaves a gap in the group of older physicians in the province.

Dr. Hugh Allan Stevenson, of London, Ont., died on May 27, 1942. He was about 72 years of age. Dr. Stevenson was mayor of London for three terms, 1915-17, and had served on every civic body except the Board of Education. At the time of his death he had been a member of the Public Utilities Commission since 1935. He was a son of Hugh Stevenson II who came to Canada from England and settled in London about 1816. Dr. Stephenson graduated in Medicine from Trinity University, Toronto (1895), and did post-graduate work at McGill. He became a captain in the Militia in 1914, and joined the Canadian Expeditionary Force, being promoted to Major and was stationed at Valcartier with a Field Ambulance unit.

News Items

Alberta

At the last meeting of the Council of the College of Physicians and Surgeons of Alberta the question of Provincial life insurance was up for discussion. It was unanimously resolved, that the Registrar send a letter to all members of the profession, explaining its stand on refusing to sanction a fee of less than $5.00 for a complete insurance medical examination.

At the last session of the Legislature an increased grant of $30,000.00 was made toward the expenses of the two clinics, one in Calgary, and one in Edmonton, in anticipation of surgical treatment being given to cancer patients. There has been some discussion as to who should perform the operation in cases when recommended. The general feeling of the profession throughout the Province is that any skilled surgeon could be chosen by the patient and that a referred patient should be sent back to the surgeon who was the patient's choice.

The demand is ever increasing for the establishment of psychopathic wards in certain city hospitals, but owing to war conditions the Provincial Government, while believing in the principle, feels that the time is not opportune for the extra expenditure.

The University of Edmonton has, with the assistance of the College of Physicians and Surgeons, developed a fine medical library of the most recent and authoritative works and many of the leading medical journals. The use of the books is free to members of the profession throughout the Province, the only stipulation being, the person receiving the book must pay the postage. While not as many members of the profession, as one would like, avail themselves of this privilege, the number of those doing so is gradually increasing.

Some health units in the Province are working very strenuously to reduce the incidence of tuberculosis in human and domestic animals, and are co-operating with the Federal Department of Agriculture. Students in high schools and teachers are taking tuberculin tests. There is a growing feeling that patients with open tuberculosis should not be permitted to leave institutions and return to their homes, no matter how strongly they so desire.

The question has been raised whether a hospital should not permit any surgical operation, of a major nature, without the written consent of the patient or of some one in authority to speak for him, but so far no hospital regulation has been made in this regard.

The Government has recently been requested to make provision for the establishment of old folks' homes, where senile patients and epileptics could be sent and thus relieve the general hospitals throughout the Province. It is felt that were such established, the cost of per capita upkeep would be much less than at present. The homes would be supported largely by the municipalities or the individual families paying for the care of their patients. As our municipalities in Alberta are small, no one seems willing to finance the project, and the Provincial Government feels that it cannot undertake it, at the present time.

G. E. LEARMONTH

British Columbia

Doctor Wallace Wilson, of Vancouver, who is known throughout Canada for his work on Medical Economics, has recently joined the Army. He is to be District Medical Officer of Military District No. 11. Doctor W. A. Clarke, of New Westminster has also joined the Services, and will be associated with Doctor Wilson. Organized Medicine in British Columbia and indeed throughout Canada will be very greatly the loser through the absence of these two men, but *c'est la guerre.*

The nursing situation in British Columbia is becoming very serious, as we imagine must be the case everywhere in Canada. Recently, the Vancouver General Hospital, through its Supervisor of Nurses, Miss Grace Fairley, R.N., has been appealing to the medical profession to co-operate in every way in order to relieve the heavy load that is thrown on the nursing staff, partly through a very definite increase in work, partly through the absence of a great many nurses, and the great difficulty of obtaining replacements. One large ward in this hospital has already been closed and various schemes for doubling up are being tried. We imagine that things will get worse instead of better. The increase in the birth rate alone has thrown a tremendous extra load on all hospitals. The public has become thoroughly used to the idea of hospitalization in case of maternity, and it will be very difficult to return to home confinements, but we imagine this may yet have to come.

We congratulate Doctor W. B. Burnett, of Vancouver, on the honour he has attained through nomination for Senior Membership in the Canadian Medical Association.

Medical Boards, under the Department of National War Services, have been appointed at Vancouver, Victoria, Nanaimo, Prince George, Prince Rupert, Trail, Cranbrook, New Westminster, Kamloops and Penticton. In the preparation of the nominations submitted, the district medical associations had an opportunity to select the names. The Canadian Medical Association passed the nominations as collected to the Department of National War Services, by whom appointments were made.

We imagine it must be something of an innovation but, nevertheless, we feel that an excellent step has been taken by the staff of the Nanaimo Military Hospital, who have initiated a series of bi-monthly clinical meetings, to which the civilian doctors are welcomed. A good many of the men on the staff are specialists of high standing in their own communities and the agenda of these meetings read very well. We should think that they must be of great interest and value.

At the time of writing, medical men in British Columbia are looking forward to the Canadian Medical Association convention, which many of them are attending. The program promises to be an extremely good one.

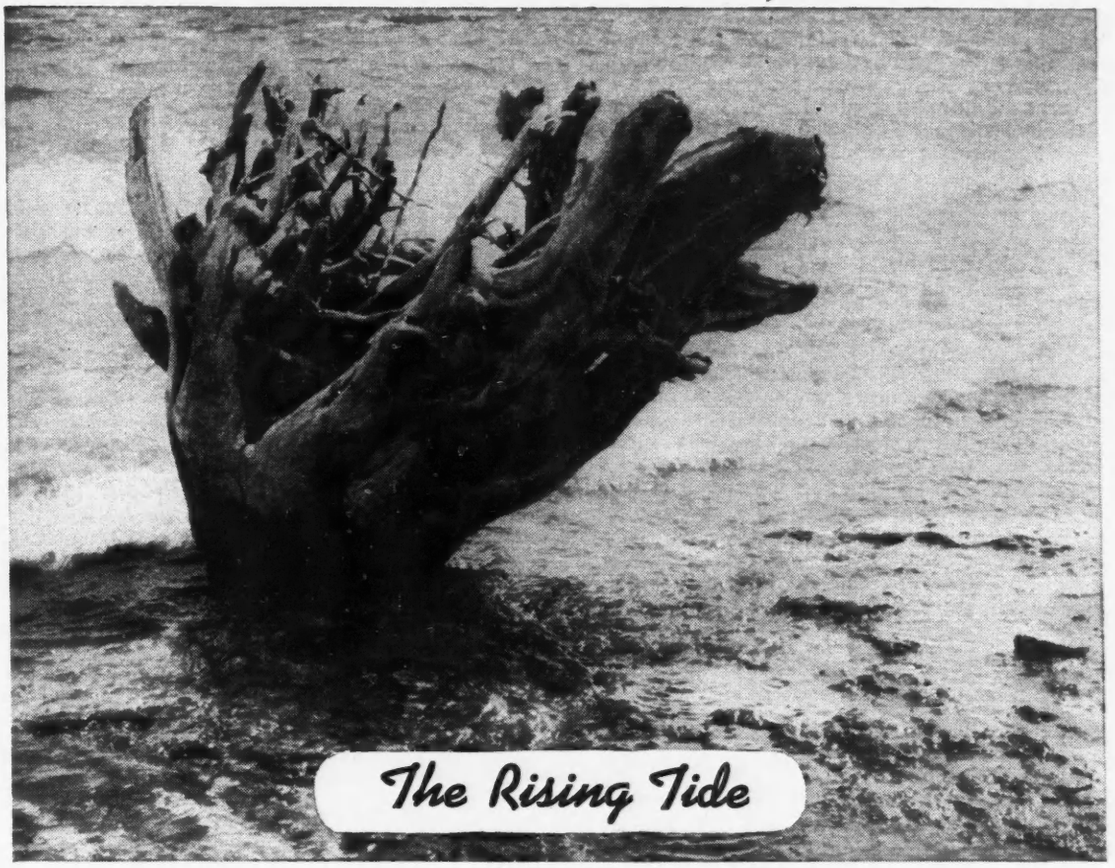
The following have left for Air Force training in Eastern Canada: Doctors B. F. Bryson, formerly on the staff at Essondale; H. L. Dobson, formerly an intern at the Royal Jubilee Hospital, Victoria; T. J. Durkin, formerly an intern at St. Joseph's Hospital, Victoria; M. R. Earle, formerly an intern at Vancouver General Hospital; G. R. F. Elliot, formerly Medical Officer at Quarantine Station, William Head; A. Hebert, formerly an intern at St. Paul's Hospital, Vancouver; F. L. Skinner, formerly in practice in Vancouver; J. F. Sparling of Haney; W. D. Sharpe, formerly at Zeballos; R. C. Talmey, formerly an intern at St. Paul's Hospital, Vancouver, and N. Woywitka, formerly an intern at St. Joseph's Hospital, Victoria.

J. H. MACDERMOT

Manitoba

Dr. Bruce Chown, superintendent of the Children's Hospital, has informed the civic health committee that the hospital is considering the expansion of its facilities by putting in eight more beds and fitting up an additional dressing room. If this expansion is carried out, the hospital will turn the former milk depot into living quarters for interns.

Dr. William Turnbull has been named temporary director of Winnipeg's new division of medical care. His chief business will be to investigate all applications for free public ward treatment in city hospitals. The post carries with it a salary of $4,000 per year.



Like the tide at flow, every wave rising just a little higher than the last, so the symptoms of the climacteric, slight at first, gradually increase in severity. "Emmenin" therapy, instituted when the menopause first manifests itself, will usually alleviate the symptoms and subsequently keep them under control. If the syndrome is well established before treatment is begun, "Premarin" is recommended to bring the severe symptoms under control quickly. Clinical investigation indicates that this new product is the most potent orally-active natural oestrogen so far discovered.

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Dr. Ada I. Wallace, medical health officer for Emerson and the rural municipalities of Franklin and Montcalm, has been appointed by the Manitoba Government as coroner. She is the wife of Rev. H. B. Wallace, United Church pastor at Emerson. A 1922 graduate of the University of Manitoba Medical College, Dr. Wallace was born at Gladstone, Man. She served one year as an interne at Misericordia Hospital.

Formerly head of medical boards of M.D. 10, Lieut.-Col. Andrew M. Davidson, R.C.A.M.C., heads a Canadian army medical board set up in Washington, D.C., to examine Canadians living in the United States who are subject to the United States draft law but prefer to serve in the Canadian Army.

Major Ross Cooper, R.C.A.M.C., has been appointed Commanding Officer of No. 3 Casualty Clearing Station with the rank of Lieut.-Colonel. He left Winnipeg in 1940 as adjutant of No. 5 Canadian General Hospital, and has recently returned from England. Major Jack McKenty, R.C.A.M.C., will be second in command.

ROSS MITCHELL

New Brunswick

Dr. E. A. Petrie was the special speaker at the graduation exercises of the training school for nurses at St. Joseph's Hospital, Saint John. Dr. Petrie laid new emphasis on the necessity for continued reading by nurses after graduation, to assure progress and maintain quality in nursing service.

Dr. A. D. Gibbon recently joined the Air Force Medical Service and is at present taking special courses in upper Canada.

The New Brunswick delegation to the Canadian Medical Association Annual Meeting at Jasper will be small this year due to the fact that the whole profession is overworked consequent upon the large number of enlistments in the active forces. At present it is known that Dr. A. F. VanWart, Dr. Geo. White, Dr. Geo. Skinner and Dr. L. De V. Chipman will attend.

Col. Geo. Lyons has returned to his home in Moncton from Overseas. It is anticipated that Col. Lyons will undertake instructional duties in Canada.

At the meeting of the college in St. Paul in April, Dr. A. T. Leatherbarrow, of Hampton, was made a Fellow of the American College of Physicians.

Dr. A. F. VanWart, of Fredericton, was elected President of the Alumni Society of the University of New Brunswick at the recent ancænia.

It is no novelty to hear of a physician taking an interest in agriculture in some cases in a small way, and occasionally one of greater wealth has made the gesture as a gentleman farmer. In southern New Brunswick during the past several years quite a number of doctors have bought more or less abandoned farms within motoring distance of their town practices. Some live the year round on new acres, others spend the more pleasant summer months in rural scenes and hibernate in town during the months of tough going. The money and time previously spent on golf are now lavished on flowers, vegetables, chickens, apple orchards, reforestration, field crops and it is reported that one such man is even possessed of a Jersey calf. Anything may happen now and perhaps will. The conversation in the staff room of certain hospitals is now a pleasant mixture of insect sprays, poultry foods and sulpha drugs. The bragging has switched from low handreaps to high egg production and the odds against the planter of any special elm tree ever sitting in the shade of same, taking into consideration the ravages of coronary disease, income tax and ordinary wear and tear inherent in making a living in the practice of medicine.

The *Royal Gazette of New Brunswick* published new regulations respecting the control of venereal disease in the first week of June. Their new regulations are the result of a new study initiated due to new conditions resulting from the present war. Previously, there were several weak points in the law on this subject and an attempt has now been made to close the gaps and so to provide for the prevention, treatment, mitigation and suppressions of social diseases.

A. STANLEY KIRKLAND

Nova Scotia

The Dalhousie Medical School Class of '98 was a good sized class for its time. Last month it held a reunion with all surviving members present. They were Dr. A. McD. Morton, of Halifax, Dr. G. G. Gandier, of Dartmouth, N.S., Dr. Edward M. MacDonald, of Sydney, C.B., and Dr. Matthew G. Archibald, of kamloops, B.C.

Following the local lead of Halifax practitioners, doctors of Glace Bay, Pictou, and other towns are moving toward the elimination of evening office hours and the better control of their routine work. In Halifax even the most sanguine protagonists of the scheme admit surprise at the unqualified success of their efforts.

Dr. Roy Maxwell, of Glace Bay, has been appointed radiologist to a group of Cape Breton hospitals, including the Glace Bay General, the Hamilton Memorial, the New Waterford General and the Harbour View hospital.

Dr. Arthur Ormston (Dal. '42) has been appointed part time Medical Health Officer at Sydney.

Dr. Robert MacLeod (Dal. '25), of Upper Stewiacke, is moving to Halifax.

More heated than ever is this year's discussion by the local profession on the good or harm to come from bathing in Halifax's North West Arm. The temperature of the argument keeps step with Dr. D. J. MacKenzie's increased *B. coli* count, with the added refuse from augmented harbour traffic and the multiplying houses on the Arm's once birch-clad slopes. Are the risk of sinusitis and otitis media greater evils than sagging recti and sloping deltoids? Are not the salt sea and sunlight powers of antisepsis? Is not the metabolic stimulant of a swim a good antitoxin? Thus argue the doctors, while Halifax city fathers, as in pre-war years, complacently watch the inevitable approach of ruin to one of the most beautiful watering spots on this continent.

ARTHUR L. MURPHY

Ontario

On Thursday, May 21st, a delightful tribute was paid to the long years of service of Dr. George Dana Porter as a Director of the Student Health Service of the University of Toronto.

Dr. Porter served as the first Director of this Service in 1921 which he administered until his retirement in 1941. His friends in the University felt that his work had been so outstanding in the field of Public Health and Preventive Medicine that the successful accomplishment of his work in the Student Health Service should be marked in some special way. At a dinner in his honour on the above date, a plaque was presented to the University on behalf of his friends. This was accepted by President Cody and will be placed on the walls of the building housing the Student Health Service. The plaque reads: "In honour of George Dana Porter, M.B., pioneer in Public Health in Canada who served his University with de-

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voted interest as Director of the Student Health Service, from its inception until his retirement, 1921-1941.''

About seventy-five University friends and associates were in attendance, with Dr. J. H. Elliott in the Chair. The toast to the guest was proposed by Professor A. Hunter, and to this Dr. Porter responded in his very best way. He was literally on his toes, holding the audience spell-bound. Dr. Porter has been known as an excellent speaker. Those that were permitted to be present feel that never did he make such an excellent address as on this occasion.

Following the presentation of the plaque by Dr. Wasteneys the President Dr. Cody, replied.

Reference was made by the Chairman to Dr. Porter's athletic record. He was for three years a member of the Service Association Football team. For three years, 1891-1892-1893 he was all-round track champion, a record which has never been equalled. He was a member of the Athletic Directorate for twenty years and has been a member of the Athletic Advisory Board for forty years.

Further honour was paid to Dr. Porter by the Canadian Public Health Association at its annual meeting in June, when he was elected Honorary Life Member as a tribute to his work in Public Health, and in particular his long interest in the work of the Association.

Toronto East Medical Association has appealed to the public to co-operate in eliminating unnecessary calls, in the following statement which has been distributed to householders in East Toronto. ''There is a general belief that physicians do not come under the gasoline rationing regulations. On the contrary, we are allowed insufficient gasoline for our usual mileage required for day and night, house and hospital calls, with no allowance for pleasure.

''Your co-operation in coming to the doctor's office when possible, and sending in your house calls early, preferably before 10 a.m., and advising us of the urgency of the call, would enable us to organize our work to avoid unnecessary driving. All emergency calls will receive the usual attention. Your assistance during the present crisis is imperative.'' The statement is signed, ''Toronto East Medical Association.''

The city of Brantford has made a move to put into practice lessons deduced from the recent report of Dr. Ebbs, of the Hospital for Sick Children of Toronto, on the relation between malnutrition and maternal and infant deaths. Medical Officer of Health Dr. Hutton has asked that there be placed in the public health estimates the sum of money necessary to supplement the diet of expectant mothers.

Every expectant mother in Brantford who is found by her family physician to have a poor diet (as measured by Dr. Ebbs' standard) is entitled daily to receive from the city the following supplement to the food she gets in her own home; one egg; 30 ounces of milk; 4½ ounces of canned tomatoes; ¼ ounce of cheese; one orange; and two teaspoonfuls of cod liver oil or its equivalent in concentrate.

We learn that the Associated Medical Services Incorporated is organizing a branch in Orillia.

Dr. W. Douglas Piercey Assistant Superintendent, and Acting Superintendent during the enforced absence, because of illness, of Dr. Dobbie, has been appointed Superintendent of the Ottawa Civic Hospital in succession to Dr. Dobbie.

The Donald C. Balfour Lectureship in Surgery, of the University of Toronto was delivered on May 22, 1942, by Dr. Alfred Blalock, Professor of Surgery, Johns Hopkins Hospital School of Medicine.

In the list of the King's Birthday Honours appears the name of Dr. Alexander Francis Mahaffy, 51, Canadian-born director of the Yellow Fever Research Institute in Uganda, who was awarded the rank of Companion of St. Michael and St. George.

Mr. Mahaffy was born in Mitchell, Ontario, in 1891; he received his B.A. from University College in 1912, then went to the Yukon to teach high school in Dawson City. He enlisted in 1916 in the 4th Canadian Yukon Infantry Corps, later transferred to the 2nd Batt. Machine Gun Corps. He saw action at Paschendaele, Amiens, Cambrai, Valenciennes and Mons, and was gassed at Arras 1918. Returning to Canada after the war he entered the medical course, graduating M.D. 1923, when he joined the Rockefeller Foundation, staying until 1934. He then took the public health course in the University of Toronto, graduating with his D.P.H. in 1935. He was an intercollegiate champion wrestler while at Varsity. The award was made because of his extensive work in tropical diseases and particularly as Director of the Yellow Fever Research Institute in Uganda.

Among others elected on April 30th as Fellows of the Royal College of Physicians of London were, Dr. Roger I. Lee, of Boston, President of the American College of Physicians; Dr. Ernest Jones, of London, Eng., formerly of the Department of Medicine, University of Toronto; Dr. H. H. Hyland of the University of Toronto; Dr. J. H. Palmer, of Montreal. J. H. ELLIOTT

Quebec

Ce que coûte la tuberculose à la province:

''La grande majorité de nos comtés ruraux, soit 62 sur 73, sont maintenant organisés en unités sanitaires et bénéficient des avantages de la clinique ambulante de tuberculose qui visite chaque comté au moins une fois par mois'', déclarait dans une conférence sur ''les méfaits de la tuberculose dans nos campagnes'', le docteur Lasalle Laberge, chef de la division de la Tuberculose au ministère provincial de la Santé et du Bien-Etre Social.

''Avec cette organisation provinciale, dit-il, nos campagnes sont presque aussi bien favorisées que les villes pour le dépistage de la tuberculose. Notre province paie encore chaque année à cette maladie un tribut beaucoup trop lourd qui sape les forces vives de la nation.

''En 1939, sur un total de 2,680 décès par tuberculose, 1,476 personnes, dont 656 du sexe masculin et 820 du sexe féminin, devenaient les victimes de cette maladie, entre les âges de 20 à 45 ans. Les économistes évaluent à dix mille dollars la valeur de rendement d'un jeune homme à 20 ans et à six mille dollars celle d'une jeune femme. Notre province a donc perdu de ce chef pour l'année 1939 seulement, une valeur de rendement égale à $11,500,000. Sans faire mention des inquiétudes, des complications et des tristesses morales qui accompagnent généralement la disparition d'un être encore dans la force de l'âge.''

Le docteur Laberge insiste ensuite sur la difficulté de la lutte contre la tuberculose et sur ''l'absolue nécessité'' de faire disparaître de notre province le terrible fléau. ''Une expérience conduite dans une ville des Etats-Unis, en 1917, dit-il, établit les données suivantes: pour chaque décès annuel par tuberculose, on a révélé l'existance de 18 cas de tuberculose, dont 9 souffront de maladie active, donc contagieuse dans la plupart des cas, et 9 de maladie chronique, c'est-à-dire sans activité et ne crachant plus de bacille. Pour chaque cas actif, il y a trois contacts. En ajoutant à ces 9 cas actifs les cas décédés, nous trouvons dix sources de contamination, et en multipliant par trois, le nombre des contacts s'élève à 30 pour chaque décès. Maintenant, faisons le calcul pour notre province: en multipliant 2,500 décès annuels par 18, nous aurions 45,000 tuberculeux dont la moitié, soit 22,500 sont des sources de contagion; comme trois personnes sont exposées à chacune de ces sources de contagion, nous avons un total de 67,500 personnes exposées à recevoir des doses plus ou moins fortes de bacilles tuberculeux, si nous ne prenons pas les dispositions voulues pour protéger notre population contre cette contamination possible.'' JEAN SAUCIER

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MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858

General

The American Congress of Physical Therapy.—Will hold its twenty-first annual scientific and clinical session, September 9, 10, 11 and 12, 1942, inclusive, at the Hotel William Penn, Pittsburgh, Pa. The annual instruction course will be held from 8.00 to 10.30 a.m., and from 1.00 to 2.00 p.m. during the days of September 9th, 10th and 11th and will include a round-table discussion group from 9.00 to 10.30 a.m., Thursday, September 10th. The scientific and clinical sessions will be given on the remaining portions of these days and Saturday morning. All of these sessions and the seminar will be open to the members of the regular medical profession and their qualified aids. For information concerning the seminar and program of the convention proper, address the American Congress of Physical Therapy, 30 North Michigan Avenue, Chicago, Illinois.

On account of the unsettled world conditions, the Council of the **American Association for the Study of Goitre**, has deemed it wise to cancel the annual meeting which was scheduled for June 1, 2 and 3, 1942, in Atlanta, Georgia.

We hope we will be able in the near future to assemble again, and to celebrate with a "Victory" meeting.

T. C. DAVISON,
Corresponding Secretary.

Book Reviews

Physiology for Pharmaceutical Students H. H. Barber, 2nd ed., 526 pp., illust. $4.50. Macmillan, Toronto, 1942.

Wisely, it has been decided in Great Britain that all pharmacists should have a knowledge of the actions of the drugs he sells, and that this should no longer be a mere classification such as was common in the old teaching in Materia Medica, which in Medicine became extinct years ago, but a real knowledge of pharmacology based on an adequate knowledge of physiology. Consequently, there has been a real demand for a work of this type and hence a second edition in four years. One can say safely that it is a simple, ample, well-written book for the readers it is meant to reach. The reviewer considers it unfortunate that the pharmacology has been divorced from the physiology and that too many old-fashioned words are still employed in this section. For this class of student, combining the pharmacology of the organs with their physiology has the advantage pedagogically that it makes the physiology real and useful to the student.

Sternal Puncture. A. Piney. 77 pp., illust. $3.75. Macmillan, Toronto, 1942.

This monograph summarizes our knowledge of the marrow cell-picture in health and disease. In a brief introduction, reference is made to the monophyletic and polyphyletic theories of blood-cell formation. The author suggests the term, "hæmaton" for the whole of the blood and blood-forming system, and divides the hæmaton into the "leucon" and the "erythron". The first chapter is devoted to a description of the various primitive and differentiated cells which may be seen in films from sternal marrow. The author, inclining to the monophyletic theory, suggests that the red and white corpuscles are derived from the hæmocytoblast which is a product of the hæmohistioblast of Ferrata. However, it is indicated that there is no certainty that there is any such cell as the hæmohistioblast, and that many hæmatologists believe that the hæmocytoblast is identical with the myeloblast, which is a cell giving origin only to the granular leucocytes. The seven following chapters deal with the changes in the "myelogram" or marrow-cell picture in the leukæmias, leukamoid conditions, tumours of the bone marrow, the anæmias, erythræmia and allied states, infective diseases and some protozoal diseases. The technique of sternal puncture is described in the appendix. There is one coloured plate showing the marrow cells in health and in pernicious anæmia.

The author writes clearly and the book should be of interest to internists and laboratory workers.

Skin Grafting. E. C. Padgett. 149 pp., illust. $4.50. C. C. Thomas, Springfield, 1942.

Excellent paper is used. The illustrations are quite good.

This book is the written enthusiasm of an artist for his work: the pleasure which comes when a new tool aids in the ability to do more exact and more satisfactory work. He has used the dermatome distributed by the Kansas City Assembly Company for the past three years. Sheet skin grafts are classified, in microscopic examination, for clinical use as (1) Thiersch; (2) Superficial Intermediate, one-half to two-thirds of the skin in depth; (3) three-quarters thickness, which includes 75 to 90 per cent of the skin; and (4) full thickness. He reports upon 68 cases of 2 and 137 cases of 3 done in the years 1938 to 1940. He has been able (*a*) to select a predeterminable thickness of sheet; (*b*) to cut at a uniform depth; (*c*) to obtain large size sheets from regions not previously available; (*d*) to obtain more exact knowledge of skin thicknesses at various ages; (*e*) to decrease the operating time where large areas are to be covered; (*f*) to decrease the number of operations in individual patients; (*g*) to increase the percentage of "takes"; (*h*) the facility in grafting body cavities and sulci; (*i*) to use superficial intermediate or three-quarters (deep intermediate) sheets where previously skin flaps had to be used. The book covers the field of skin grafting and should be of help to the surgeon who has a desire to improve his technique.

The Eye Manifestations of Internal Disease. I. S. Tassman. 542 pp., illust. $11.00. McAinsh, Toronto, 1942.

It is some time since a book dealing with the relationship of the eye to general disease has appeared on the market. Hence, this volume is timely. The subject is dealt with in a very lucid, smoothly-running style, that makes for easy reading. It covers the subject material of the field very completely, though one would wish, sometimes for more detail. In many instances, the different disease entities are handled in a descriptive way, with little or no discussion of the etiology and functional pathology. Apparently it was not the intention of the author to make the book "encyclopædic". It is felt that the value of the work would have been enhanced with the inclusion of such material. As a rule the book is well illustrated, though some of the illustrations are markedly below the general level of quality. None the less, it forms an important link between general medicine and ophthalmology. As such it is of distinct value both to the student of ophthalmology and of medicine.

Diseases of the Nose, Throat and Ear. I. S. Hall. 2nd ed., 446 pp., illust. Macmillan, Toronto, 1941.

Diseases of the Nose, Throat and Ear does not fulfil the author's aim stated in the preface, that it is "designed to meet the needs of the busy practitioner and the student". It is rather poorly balanced and elementary. The nasal anatomy is sketchy and the nasal physiology unconvincing and uninteresting. Pages are spent describing details of the most elementary examinations, which are common knowledge and better learned by demonstration in the final student years. The handling of nasal fractures, an important subject to busy practitioner and student, is inaccurate and misleading, while the operation of submucous resection of the septum, by comparison of little interest to the busy practitioner and student, is described in detail. The section on the pharynx and nasopharynx is also sketchy and inaccurate, but improves in its description of the adenoid and its diseases, which is adequate and to the point. Passing into the final two sections, the volume "warms up". The chapter dealing with the larynx and endoscopy is better, while the section on the ear is quite good. With a considerable revamping of the first half, the volume could be recommended to busy practitioners and students.